Molar Pregnancy: A Case Study

By: Kathryn Ackerman, RN MSN WHNP
Objectives

- Learner will be able to identify the four types of gestational trophoblastic disease.
- Learner will be able to identify initial care steps and treatment for patients with hydatidiform moles.
- Learner will be able to identify initial steps for patients with postmolar gestational trophoblastic neoplasia.
- Learner will be able to identify staging and proper treatment modalities for patients with gestational trophoblastic neoplasia.
Gestational Trophoblastic Disease (GTD)

- 4 clinicopathologic forms
  - Hydatidiform Moles (complete & partial)
  - Invasive Moles
  - Choriocarcinomas
  - Placental site trophoblastic tumors (PSTT)

- Gestational Trophoblastic Neoplasia – Invasive Moles, Choriocarcinoma, & PSTT

- Can Progress, Invade, Metastacize, & Lead to Death when untreated
Hydatidiform Moles

- **Incidence**
  - 1 per 1,000-1,200 pregnancies in North America, Australia, New Zealand, & Europe
  - Up to 2.0 per 1,000 pregnancies in Southeast Asia & Japan
  - Up to 20% of these will require treatment for malignant sequelae

- **Risk Factors**
  - American Indians, Eskimos, Hispanics, African Americans, & Asians
  - Extremes of maternal age
    - >35 or <21 risk is 1.9 times higher
    - >40 risk is 7.5 times higher
  - Prior molar pregnancy – 10-20 times greater than general population
  - Familial clusters are associated with novel missense NLRP7 gene mutation on chromosome19q
  - History of SAB – 2-3 times greater than women with no previous SAB
Pathophysiology of Hydatidiform Mole

Moles are caused by varying degrees of trophoblastic proliferation and swelling of placental villi associated with an absent or abnormal fetus/embryo. The trophoblast is consistently hyperplastic with varying degrees of atypia, and villous capillaries are absent.

~90% complete moles are 46XX

Originate from duplication of a haploid sperm after fertilization of an egg in which the maternal chromosomes are either inactive or absent.

The remaining 10% result from fertilization of an empty ovum by 2 sperm (may be 46XY or 46 XX)

Most partial moles have a triploid karyotype, resulting from fertilization of an apparently normal ovum by 2 sperm (usually 69XXY)

Of complete moles, 15-20% will continue on to develop GTN, whereas <5% of partial moles do.
Typical Presentation of Complete Moles

- Vaginal bleeding between 6-16 weeks in 80-90% of cases
- hCG levels $>100,000$
- Absent FHTs
- Uterine enlargement $> dates$ (28%)
- Hyperemesis (8%)
- PIH in the first or second trimester (1%)
- Bilateral theca lutein cyst enlargement ($>5-6$ cm) of the ovaries (15%)

All but the first 3 symptoms occur less frequently due to early diagnosis resulting from the increased use of early ultrasounds
Presentation of Partial Moles

- Generally present as incomplete or missed abortion
- Diagnosis usually made histologically after D&C
- Bleeding (75%)
- Other symptoms of complete moles are rare
- Preevacuation hCG levels are only >100,000 in 10% of partial moles.
Invasive Moles

- **Incidence**
  - 10-17% of hydatidiform moles
  - 15% metastasize to the lungs or vagina

- **Patho** – benign tumor that arises from myometrial invasion of a hydatidiform mole via direct extension through tissue or venous channels

- **S/S – (same for choricarcinoma)**
  - Persistent hCG elevation after evacuation of hydatidiform mole
  - Irregular bleeding after evacuation of molar pregnancy
  - Enlarged, irregular uterus
  - Persistent bilateral ovarian enlargement
  - Presence of metastatic vaginal lesions (can bleed uncontrollably)
Choriocarcinoma

**Incidence**
- North America & Europe: 1 in 40,000 pregnancies; 1 in 40 hydatidiform moles
- Southeast Asia: 9.2 per 40,000 pregnancies
- Japan: 3.3 per 40,000 pregnancies
- Can occur after ANY pregnancy event
  - 25% after abortion or tubal pregnancy
  - 25% after normal term/preterm gestation
  - 50% after hydatiform moles (though only 2-3% of moles progress to choriocarcinoma)

**Risk Factors**
- Previous complete mole: 1,000 times that of any other pregnancy event
- Asians, American Indians, African American
- Advanced Maternal Age
- Long term oral contraceptive use
- Blood Group A
Choriocarcinoma (cont’d)

- Patho – malignant disease characterized by abnormal trophoblastic hyperplasia and anaplasia, absence of chorionic villi, hemorrhage, and necrosis, with direct invasion into the myometrium, and vascular invasion resulting in spread to distant sites
- Mets to lungs, brain, liver, pelvis, vagina, kidney, spleen, and intestines
- S/S: Same as Invasive moles
- Persistently elevated hCG levels after evacuation/delivery
- Postpartum bleeding & subinvolution
- If associated with nonmolar gestation, there are no characteristic signs or symptoms. Those that do occur are associated with invasion of the tumor in the uterus or metastasis.
- Pain from uterine perforation, hemoptyis, melena, evidence of intracranial pressure from intracerebral hemorrhage leading to headaches, seizures, hemiplegia, dyspnea, cough, chest pain
Placental Site Trophoblastic Tumor

- Incidence — extremely rare
- Patho
  - Tumors that arise from the placental implantation site
  - Consists mainly of mononuclear intermediate trophoblasts without chorionic villi infiltrating in sheets or cords between myometrial fibers
  - Assoc with less vascular invasion, hemorrhage & necrosis than choriocarcinoma
  - Propensity for metastasis
  - Immunohistochemical staining reveals the diffuse presence of cytokeratin and human placental lactogen, but only focal hCG
  - More often diploid than aneuploid
  - Most follow nonmolar gestations
  - Epithelioid Trophoblastic Tumor — rare variant of PSTT, simulates choriocarcinoma, can occur many years after a full term delivery
- S/S
  - Irregular uterine bleeding (often distant from last pregnancy)
  - Rarely: nephrotic syndrome, virilization
  - Uterus symmetrically enlarged
  - Only slightly elevated hCG levels
Diagnosis

- Ultrasound
- HCG levels
- Pathology
Ultrasound

- Characteristic pattern in complete moles
- Hydropic swelling leads to vesicular pattern: multiple echoes (holes) within the placental mass
- No fetus

- Partial Moles: focal cystic spaces within the placenta; increase in transverse diameter of the gestational sac
- These signs may be subtle or lacking in early pregnancy in both complete & partial moles
Classic Ultrasound Images
Human Chorionic Gonadotropin

Why hCG?
- Disease specific tumor marker produced by moles & GTN
- Easy to measure: blood or urine
- Levels >100,000 suggest increased risk of complete mole, as well as correlation with extent of disease
- Clinical diagnosis of GTN most often made through serial hCG levels, with a continued rise or plateau in hCG levels after evacuation of the mole
Phantom hCG Levels/False Positive Results

- Use assay that will detect all 6 variants of hCG
- Can be as high as 800 mIU/mL
- Result from proteolytic enzymes that produce nonspecific protein interference and heterophile (human antimouse) antibodies which can mimic hCG immunoreactivity

To rule out Phantom hCG:
- Determine urine hCG level (should be negative because interfering substances do not appear in urine)
- Request serial dilution of serum (which will not show a parallel decrease in hCG)
- Send serum & urine to an hCG reference lab for further testing
  - Can also be caused by LH crossreactivity with hCG. Measure LH levels, and if needed an OCP can suppress the LH levels to ensure an accurate hCG level before beginning treatment for GTN.
Pathologic Diagnosis

- P57 staining
  - Absent in complete moles
  - Positive in partial moles (also in hydropic fetuses)
- Flow cytometry
  - Curettage, biopsy of metastatic lesions, or examination of hysterectomy samples or placentas
  - Biopsy of vaginal lesions may bleed heavily
Pt is a 28 y/o MWF who presented to office on February 21 for initial pregnancy exam.

LMP Dec 12, putting her at 10 weeks gestation.

Pt was attempting pregnancy

Pregnancy symptoms: Amenorrhea, Breast tenderness, Fatigue
Patient History

- **OB Hx:** G2P0010; SAB 3/2011

- **Medical Hx:** Past HPV; Chlamydia tx in 2004; Childhood asthma (stopped all meds at age 10)

- **Surgical Hx:** LEEP in 2007

- **Family Hx:** Denies family history of heart disease, diabetes, or cancer

- **Genetic Hx:** Denies genetic problems in her or baby’s father’s family

- **Social Hx:** Married 2 years, Denies smoking or Illicit drugs; Drinks socially (none since pregnant); Exercises 3-4 times a week (gym classes)

- **Current Medications:** Prenatal vitamin w/DHA q day

- **Allergies:** NKDA
Objective Info

Ht: 5’ 8”   Wt: 136   BMI: 20.7

UA: WNL (Negative for protein, nitrites, WBC, ketones, blood)

Physical Exam: Initial pregnancy exam was conducted, including breast exam, heart & lung auscultation, abdominal palpation, inguinal nodes, and pelvic exam (bimanual & speculum). The exam was WNL, with the exception of an 8-9 week uterus
Initial Ultrasound

Initial ultrasound was as follows:

- No heartbeat
- Gestational sac present
- No obvious fetus
- Possible diagnoses:
  - Missed Abortion
  - Partial mole
Work Up for Suspected Mole

- Labs to help r/o medical complications (anemia, preeclampsia, hyperthyroidism)
  - CBC w/platelets, coag panel, basic chemistry, hepatic, kidney & thyroid panels, UA, Blood T&C, pretherapy serum hCG
- Chest xray
- Evacuation of Mole – suction d&c; hyst (even with hyst, must follow Hcg)
Twin Pregnancy

- Diagnose viability of unaffected twin with ultrasound &/or cytogenetics.

- Up to 40% of pregnancies will result in normal, viable fetuses if allowed to continue, but with heavy risks (increased risk of hemorrhage & medical complications, as well as persistent GTN).

- Refer to MFM.
Plan

- Labs: Type & Screen, CBC
- Discuss options with pt:
  - D&C (If D&C, obtain specimen for genetic studies as this was her second miscarriage)
  - Watch & wait for bleeding
Pt chose to have a D&C as this would allow her to potentially determine the cause of her second miscarriage.

D&C done 2/23

Specimen sent to pathology, and for genetic testing
Pathology Results

- Final pathology showed Complete Mole:
  - Chorionic villi, Complete Hydatidiform Mole
  - Decidua, no inflammation, necrosis or hemorrhage
  - Placental implantation site, atypical extravillous trophoblast
  - Endometrium, hypersecretory
  - Stained negative for p57, consistent with complete mole
Classic Ultrasound Images
Next Step for this Patient

Due to the increased risk of hydatidiform moles (complete or partial) progressing to gestational trophoblastic neoplasia, serial hCG levels are drawn:

- Initial post evacuation hCG level within 48 hours
- Weekly until hCG <5 mIU/mL
- Then monthly x6-12 months

The patient will also need to start a reliable method of birth control, as Hcg levels are the only method of monitoring for progression of this disease. If she were to become pregnant during her monitoring period, there would be no way to easily detect the neoplasia.

Prophylactic chemotherapy is not recommended due to low morbidity & mortality achieved through serial hCG levels, and the risks of chemotherapy. In addition, prophylactic chemo would not negate the need for continued serial hCGs.
Repeat HCG Levels

<table>
<thead>
<tr>
<th>Date</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/1/2012</td>
<td>2571</td>
</tr>
<tr>
<td>3/6/2012</td>
<td>775</td>
</tr>
<tr>
<td>3/13/2012</td>
<td>225</td>
</tr>
<tr>
<td>3/20/2012</td>
<td>667</td>
</tr>
</tbody>
</table>
What is next?

- Elevating hCG levels is a diagnostic of gestational trophoblastic neoplasia.
- Referral to Gyn/Oncologist
  - Possibility of falsely elevated result
    - Studies show false positive unlikely if result is >200
  - Requested Stat HCG level to confirm elevation, Liver enzymes, metabolic profile, CBC
- Office visit the following day; he will order Chest Xray & abdominal CT
- Her repeat HCG was 908 (continuing to increase).
Testing with Dx of GTN

- Labs
  - CBC w/platelets, coag panel, basic chemistry, hepatic, kidney & thyroid panels, UA, Blood T&C, pretherapy serum hCG
  - Chest Xray, if negative, Chest CT
  - If chest metastases, then abdominal/pelvic
  - Abdominal/Pelvic/Brain CT or MRI to evaluate for additional metastases
Results of Pt’s Testing

This patient’s chest Xray was negative, so a CT was done revealing a 4 mm pulmonary nodule. No other metastases were found. Her next hCG level was 1800.
Staging for GTN

- **Stage I**: Disease confined to the uterus
- **Stage II**: Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligaments)
- **Stage III**: Disease extends to lungs with or without genital tract involvement
- **Stage IV**: Disease involves other metastatic sites
## Scoring System for GTN

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&lt;= 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;10,000</td>
<td>10,000-100,000</td>
<td>100,000-1,000,000</td>
<td>&gt;1,000,000</td>
</tr>
<tr>
<td>Largest tumor mass, including uterus (cm)</td>
<td>&lt;3</td>
<td>3-4</td>
<td>&gt;=5</td>
<td>-</td>
</tr>
<tr>
<td>Site of metastasis</td>
<td>-</td>
<td>Spleen, kidney</td>
<td>GI tract</td>
<td>Brain, liver</td>
</tr>
<tr>
<td>No. of metastasis</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>&gt;=2 drugs</td>
</tr>
</tbody>
</table>

Total score is obtained by adding individual scores for each prognostic factor. Low risk <7, High risk >=7.
Case Patient’s Treatment

She was classified as a FIGO Stage 3, but due to the scoring system for GTN (she scored a 1 for her single metastasis site), she was considered low risk.

As such, she was started on single drug therapy with Methotrexate on 3/27
Treatment for Low Risk GTN

- Single agent chemotherapy
  - Methotrexate 0.4 mg/kg (max 25 mg) IM or IV push daily for 5 days every other week
  - Dactinomycin (or Actimomycin D) 10-12 mg/kg IV daily for 5 days every other week
    - More side effects such as alopecia & nausea than MTX, so used less often

- Option of hysterectomy may decrease chemotherapy duration

- Treatment continued until hCG levels back to normal & then one additional dose after

- If significant elevation in hCG, development of metastases, or resistance to single agent chemotherapy, multiagent chemotherapy should be initiated

- Incidentally, this patient’s hCG level dropped to 60 after her first dose. She will receive weekly MTX injections until one week after her hCG levels normalize.
Treatment for High Risk GTN

- Multiagent Chemotherapy
  - MAC
    - Methotrexate
    - Actinomycin D
    - Cyclophosphamide OR Chlorambucil
  - EMA-CO
    - Etoposide
    - High dose methotrexate with folinic acid
    - Actinomycin D
    - Cyclophosphamide
    - Vincristine

Chemotherapy is continued 2-3 doses after hCG levels return to normal.

Hysterectomy does not decrease the duration of chemotherapy in high risk disease.

Surgery &/or Radiation may be necessary to treat complication with metastases.

For high risk patients, survival rates are 80-90%. Approximately 30% will fail first line therapy & relapse from remission, and will need additional treatments. The majority of these patients can be cured. Patients with metastases to the brain, liver, and GI tract will require more extensive treatments. Their survival rates are 75%, 73% and 50% respectively.
Follow Up after Chemotherapy

- Serial hCG levels:
  - Every 2 weeks for the 1st 3 months of remission
  - Then monthly x12 months

- Contraception (preferably OCP) x12 months after completion of chemo. This allows for continued follow up of HCG levels, as well as the elimination of any mature ova that could have been affected by exposure to cytotoxic drugs

- Relapse rate is about 3% in the 1st year. Risk of recurrence after 1 year is <1%

- Physical exams q6-12 months

  - Continued physical exams are especially necessary for patients who received etoposide containing drug combinations, as there is an increased risk of secondary malignancies such as acute myelogenous leukemia, colon cancer, melanoma, and breast cancer.
Future Pregnancies?

- Anticipate normal future pregnancies, but there is an elevated risk in subsequent pregnancies of 1-2%
- Early pelvic ultrasound to confirm normal gestation
- POC &/or placenta sent to pathology after delivery to r/o GTD
- Serum HCG 6 weeks postpartum to r/o recurrent GTN
- No increased risk of congenital malformations/complications with other pregnancies is apparent
Summary

- There are four types of gestational trophoblastic disease: Complete & partial moles, and their sequelae invasive moles, choriocarcinoma, and placental site trophoblastic tumors.

- Initial care steps and treatment for patients with hydatidiform moles: Baseline labs including hCG level, chest Xray; then evacuation by D&C, followed by serial hCG levels.

- Initial steps for patients with postmolar gestational trophoblastic disease: Repeat labs, chest Xray, chest CT if no metastases are noted on the chest Xray; CT/MRI of abdomen/pelvis, and brain if there are metastases noted on the chest Xray.

- Staging and proper treatment modalities for patients with persistent trophoblastic diseases: If low risk, treat with MTX, follow up with serial hCGs to evaluate response to therapy & recurrence. If high risk, pt will need multiagent chemotherapy – refer to specialist.
References


Questions???