Approach to Molar Pregnancy

Lee-may Chen, M.D.
Department of Obstetrics, Gynecology, & Reproductive Sciences
UCSF Helen Diller Family Comprehensive Cancer Center

Objectives

- Clinical diagnosis and staging of gestational trophoblastic disease (GTD)
- Treatment for recurrent/persistent GTD
- Future pregnancy outcomes

Epidemiology

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population risk</td>
<td>1:1000 pregnancies</td>
</tr>
<tr>
<td>U.S. population risk</td>
<td>1:1500</td>
</tr>
<tr>
<td>Taiwan population risk</td>
<td>1:125</td>
</tr>
<tr>
<td>Infertility</td>
<td>1:500</td>
</tr>
<tr>
<td>2 or more prior abortions</td>
<td>1:400</td>
</tr>
<tr>
<td>Age &gt; 40</td>
<td>1:150</td>
</tr>
<tr>
<td>Prior molar pregnancy</td>
<td>1:100</td>
</tr>
</tbody>
</table>

Molecular pathogenesis

Complete moles
- 90% 46XX, empty ovum fertilized by haploid sperm, then duplicated
- 10% XY, empty ovum with dispermy fertilization
- Mitochondrial DNA of maternal origin

Partial moles
- 90% triploid, with dispermy fertilization of normal ovum
Presentation: Classic vs. Contemporary

Vaginal bleeding
Excessive uterine size
Theca lutein cysts

Hyperemesis gravidarum
Preeclampsia
Hyperthyroidism
Respiratory insufficiency

Abnormal ultrasound
Incidental finding
Bleeding

Diagnosis

Ultrasound + hCG level

Suction & sharp D&C
Consider oxytocin, Rh immune globulin
If fertility no longer desired, hysterectomy may be considered
Chest X-ray

Molar Pregnancy Pathology

Complete mole
Circumferential trophoblast
Uniformly large villi

Partial mole
Focal proliferation of trophoblasts
Dual population of villi

Images courtesy of Dr. Joseph Rabban

Placental Site Trophoblastic Tumor

“Trophoblastic pseudotumor”
Some cured with curettage, others died of metastatic disease
Generally, hCG a less good marker
Less response to chemotherapy or radiation
Consider hysterectomy as definitive treatment
Antecedent pregnancy may be normal, molar, abortion

Images courtesy of Dr. Joseph Rabban
### Choriocarcinoma

- After 1:20-40 molar pregnancies
- After 1:40,000 term pregnancies

Antecedent pregnancies
- most likely mole

Hematogenous spread: lung, genital tract, brain, liver, kidney, GI tract
May present with (+) pregnancy test and intraperitoneal hemorrhage

![Diagram](path_to_diagram)

### Post-evacuation Follow-up

Pathologic confirmation: Mole, Choriocarcinoma, PSTT
Weekly hCG levels until normal, then follow 6-12 mo.
Contraception, pelvic examination

**Persistent disease**: Plateau or rise of hCG over 3 weeks
- Complete mole—20% persistent disease
  - 15% uterine invasion, 4% metastatic disease
- Partial mole—5% persistent disease
  - 4% uterine invasion, 0.6% metastatic disease

### Prophylactic Chemotherapy

Reduction of persistent GTD 47→14% in high risk patients by single dose of methotrexate/citrovorum
- Age > 40: 35% persistent GTD
- Age > 50: 56% persistent GTD

Consider for patients with high hCG, advanced age, or with poor follow-up

**Cons**: Low incidence of persistent GTD
- Sensitivity to chemotherapy
- Risks of chemotherapy

### Phantom hCG Results

False positive results
Possible sources: antibodies, nonspecific protein interference

Consider when clinical situation is discordant with hCG level
Confirm with urine hCG or national hCG reference laboratory
**Metastatic Work-up**

- Clinical exam
- Chest X-ray
- Pelvic ultrasound
  - If positive, CT scan
    - Abdomen/pelvis
    - Chest, Brain
- CBC, plt, hCGT, renal and liver panels
- Calculate WHO score for risk assessment

**Hysterectomy & GTD**

- Primary management, if sterilization indicated
- Uterine disease resistant to chemotherapy
- hCG follow-up still required
- Possible reduction of chemotherapy in non-metastatic disease

**Staging Systems--FIGO**

Stage I: Disease confined to uterus
Stage II: Disease limited to adnexa, vagina, broad ligament
Stage III: Disease extended to lung, no genital tract involvement
Stage IV: All other metastatic sites

**WHO Scoring System**

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≤40</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 interval</td>
<td>≤4</td>
<td>4-6</td>
<td>7-12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>hCG (mIU/ml)</td>
<td>&lt;10⁶</td>
<td>10⁶-10⁸</td>
<td>10⁹-10⁴</td>
<td>&gt;1⁰⁴</td>
</tr>
<tr>
<td>Largest tumor (incl uterine)</td>
<td>&lt;3cm</td>
<td>3-4cm</td>
<td>≥5 cm</td>
<td></td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen</td>
<td>GI</td>
<td>Liver</td>
</tr>
<tr>
<td></td>
<td>Pelvis</td>
<td>Kidney</td>
<td>Brain</td>
<td></td>
</tr>
<tr>
<td>Number of metastases</td>
<td>1-4</td>
<td>4-8</td>
<td>&gt;8</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>Single</td>
<td>Multidrug</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6 or less: low risk, 7 or more: high risk

Bagshawe, as adapted by FIGO
**GTD—Chemotherapy**

- hCG > 20,000 4 weeks after evacuation
- Rising hCG levels over 3 weeks
- Histologic evidence of choriocarcinoma
- Pulmonary metastases: >3 lesions or > 2 cm diameter
- CNS, liver, renal, GI metastases

**Non-metastatic, low risk GTD**

- Treatment
  - Single agent methotrexate
  - Single agent actinomycin-D

- 90% remission rate
- Average 8-10 weeks
- 10-20% resistance
- 2-3% relapse after normal hCG

**Methotrexate vs Actinomycin D?**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly MTX</td>
<td>53%</td>
</tr>
<tr>
<td>Daily MTX x5d q2 weeks</td>
<td>60-89%</td>
</tr>
<tr>
<td>MTX/Leukovorin x8d q2 weeks</td>
<td>69%</td>
</tr>
<tr>
<td>MTX infusion q2 weeks</td>
<td>65%</td>
</tr>
<tr>
<td>Dactinomycin q2 weeks</td>
<td>70%</td>
</tr>
<tr>
<td>Dactinomycin x5d q2 weeks</td>
<td></td>
</tr>
</tbody>
</table>

- GOG 174: Weekly MTX vs dactinomycin q 2 weeks
  - n=216, 53% versus 70%, p=0.01

**Second D&C**

- Registry study of 4050 women with persistent GTD, 1991-2000
- 544 women underwent second curettage
- 40% with no molar tissue
- 368 (68%) completed follow-up without further disease
- 116 (21%) did not require chemotherapy

- GOG 242: Phase II trial in progress
  - Pezeshki et al, Gynecol Oncol, 2004
Metastatic, high risk GTD

Combination chemotherapy
  MAC
  EMA/CO  etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine
  EP/EMA  etoposide, cisplatin, methotrexate, actinomycin-D

Over 70% remission rate, Over 90% cured
CNS: brain irradiation, intrathecal methotrexate
Liver: resection to manage complications

Lurain et al, J Repro Med, 2006
Escobar et al, Gynecol Oncol, 2003

Subsequent Pregnancy Outcome

<table>
<thead>
<tr>
<th>Prior Molar pregnancy</th>
<th>Complete</th>
<th>Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pregnancies</td>
<td>1254</td>
<td>218</td>
</tr>
<tr>
<td>Total deliveries</td>
<td>962</td>
<td>167</td>
</tr>
<tr>
<td>Term</td>
<td>68.7%</td>
<td>74.3%</td>
</tr>
<tr>
<td>Preterm</td>
<td>7.4%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>17.8%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>3.2%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Ectopic</td>
<td>0.9%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Repeat Mole</td>
<td>1.4%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Garner, Contemp Obstetr Gynecol, 2001

Pregnancy after Persistent GTD

<table>
<thead>
<tr>
<th>Total pregnancies</th>
<th>537</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deliveries</td>
<td>404</td>
</tr>
<tr>
<td>Term</td>
<td>67.8%</td>
</tr>
<tr>
<td>Preterm</td>
<td>6.0%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1.5%</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>16.9%</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>5.0%</td>
</tr>
<tr>
<td>Ectopic</td>
<td>1.3%</td>
</tr>
<tr>
<td>Repeat Mole</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Garner, Contemp Obstetr Gynecol, 2001

Pregnancy after Repeat Mole

<table>
<thead>
<tr>
<th>Total pregnancies</th>
<th>34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deliveries</td>
<td>19</td>
</tr>
<tr>
<td>Term</td>
<td>55.9%</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2.9%</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>8.8%</td>
</tr>
<tr>
<td>Elective abortion</td>
<td>8.8%</td>
</tr>
<tr>
<td>Ectopic</td>
<td>2.9%</td>
</tr>
<tr>
<td>Repeat Mole</td>
<td>20.6%</td>
</tr>
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Garner, Contemp Obstetr Gynecol, 2001
Recurrent Molar Pregnancy

At least 2 molar pregnancies
Interval of at least 6 months of normal hCG levels

<table>
<thead>
<tr>
<th></th>
<th>1st Mole</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Partial</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

Garner, Contemp Obstetr Gynecol, 2001

Recurrent Persistent GTD

N=31

1st Molar pregnancy Persistent disease
4/19 Complete 21%
0/12 Partial 0%

2nd Molar pregnancy
8/17 complete 47%
2/14 Partial 14%

Garner, Contemp Obstetr Gynecol, 2001

Pregnancy > 1 year follow-up

Retrospective review, 1985-1995
N=115
77 with spontaneous resolution of hCG
38 with resolution after chemotherapy
1 year follow-up before attempting conception
51% pregnant within 1 year after follow-up
91% pregnant within 3 years
89 Term delivery, 3 Preterm delivery, 1 IUFD, 3 Ectopics, 14 Spontaneous abortions, 5 Repeat moles
3 anomalies (heart, ?perochirus, ear)

Kim, Gynecol Oncol, 1998

Pregnancy < 1 year follow-up

Retrospective review 1966-1996
N=22
Pregnancy within 1 year of receiving chemotherapy
9 Term delivery, 1 Preterm delivery, 1 IUFD, 4 Spontaneous Ab, 1 Repeat mole
Time from chemo to conception
Term pregnancy: 9.8 months
Pregnancy losses: 6.5 months p<0.05
27% fetal loss, 4.5% GTD

Pregnancy < 1 year follow-up

Retrospective review, 1973-1998
N=43
31 complete mole, 12 partial mole
39 Stage I, 1 Stage II, 3 Stage III
Mean interval 6.3 months (1-11mo)
10 Elective Ab, 4 lost to follow-up
22 Term delivery, 3 Preterm delivery, 3 Spontaneous Ab, 1 Repeat mole
2 anomalies (polydactaly, hydronephrosis)
1 patient with metastatic choriocarcinoma, C/S @ 28wks

Subsequent Pregnancy

- 1st Trimester ultrasound—confirm intrauterine pregnancy
- Measure post-partum hCG to confirm normalization—exclude occult choriocarcinoma
- If early loss, confirm products of conception by pathology
- Routine evaluation of placenta after normal term delivery probably not indicated

Psychosocial Issues

Concurrent cancer risk with loss of normal pregnancy
Unplanned family planning
Anxiety for subsequent pregnancy

Conclusions

- hCG is a reliable tumor marker for most forms of GTD except PSTT
- GTD responds well to chemotherapy, even with advanced stage disease
- Patients with GTD can generally expect a normal subsequent pregnancy
- Subsequent pregnancies should be carefully monitored for possible recurrent GTD