Gestational Trophoblastic Disease

UCSF Obstetrics & Gynecology Update: What does the evidence tell us?

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Have you evacuated a molar pregnancy in the past 6 months?

1. Yes
2. No

38% 62%

Do you administer methotrexate for persistent GTN through your office?

1. Yes
2. No

40% 60%

Disclosure

• I have nothing to disclose
Objectives

- To describe the diagnosis and staging of gestational trophoblastic disease
- To describe the management of molar pregnancy
- To describe future pregnancy outcomes after gestational trophoblastic disease

Moles

\[ N_A = 6.02 \times 10^{23} \]

Gestational Trophoblastic Disease

- Hydatidiform mole
  - Complete
  - Partial
- Gestational Trophoblastic neoplasia
  - Invasive mole
  - Choriocarcinoma
  - Placental site trophoblastic tumor
  - Epithelioid trophoblastic tumor

Epidemiology

- General population risk 1:1000 pregnancies
- U.S. population risk 1:1500
- Taiwan population risk 1:125
- Infertility 1:500
- 2 or more prior abortions 1:400
- Age > 40 1:150
- Prior molar pregnancy pregnancies 1:100
Genetic origins of Molar gestations

GTD in Asians outside of Asia

N=3660 women with GTD, 1991-1999
Trophoblastic Screening and Treatment Centre of Northern England and Wales

322 Asian women
Incidence of GTD: 1 per 714 live births
Asians: 1 per 387
Non-Asians: 1 per 752
Asians with 1.95x higher incidence

Presentation (Classically)

84% Vaginal bleeding
28% Excessive uterine size
26-46% Theca lutein cysts

Hyperemesis gravidarum
Preeclampsia
Hyperthyroidism
Respiratory insufficiency

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

Image courtesy of Dr. Liina Poder
**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

**GTN pathology**

- Invasive Mole
- Choriocarcinoma
- Placental site trophoblastic tumor
- Epithelioid trophoblastic tumor

**Choriocarcinoma**

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

- Antecedent pregnancies
- Hematogenous spread:
  - Lung, GU/GI tract, brain, liver, kidney
- May present with (+) pregnancy test and intraperitoneal hemorrhage

**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
Post-evacuation Follow-up

Pathologic confirmation: Mole, Choriocarcinoma, PSTT
p57 immunostaining can help distinguish parental origin

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

613 women in 3 Randomized control trials
Prophylactic methotrexate or dactinomycin versus no prophylaxis
Risk of GTN: RR 0.37 (95% CI 0.24-0.57)

Studies of poor methodologic quality
Insufficient data to analyze toxicity, survival, reproductive outcomes

Fu et al, Cochrane Database Syst Rev, 2012

Metastatic Work-up

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

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Prognostic Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy interval (months)</td>
<td>2</td>
</tr>
<tr>
<td>hCG (mIU/ml)</td>
<td>4</td>
</tr>
<tr>
<td>Largest tumor (including uterus)</td>
<td>5</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>3</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>2</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>1</td>
</tr>
</tbody>
</table>

- Age <40
- Antecedent pregnancy: Mole, Abortion, Term
- Pregnancy interval: <4, 4-6, 7-12, >12
- hCG: <10, 10^2, 10^3, >10^3
- Largest tumor: <3cm, 3-5cm, >5cm
- Site of metastases: Lung, Spleen, GI, Brain, Pelvis, Kidney, Liver
- Number of metastases: 1-4, 4-8, >8
- Prior chemotherapy: Single, >2

4 or less: low risk, 5-7 intermediate risk, 8 or more: high risk

### 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

A, B, C by none, one, or two risk factors

Risk factors:
- hCG >100,000
- duration of disease > 6 months from antecedent pregnancy

### Hyterectomy & GTD

If sterilization indicated

- Uterine disease resistant to chemotherapy

- hCG follow-up still required

Possible reduction of chemotherapy in non-metastatic disease

### Phantom hCG levels

- 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
GTD--Chemotherapy

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

Non-metatstatic, 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 versus Actinomycin D

<table>
<thead>
<tr>
<th>Response</th>
<th>Weekly MTX</th>
<th>Daily MTX x5d q2 weeks</th>
<th>MTX/Leukovorin x8d q2 weeks</th>
<th>MTX infusion q2 weeks</th>
<th>Pulse Dactinomycin q2 weeks</th>
<th>Dactinomycin x5d q2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53%</td>
<td>60-89%</td>
<td>69%</td>
<td>65%</td>
<td>70%</td>
<td>94%</td>
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</table>

GOG 174: Weekly MTX vs dactinomycin q 2 weeks
n=216, 53% versus 70%, p=0.01
Osborne et al, J Clin Oncol 2011

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 closed to accrual
Pezeshki et al, Gynecol Oncol, 2004
Metastatic, high risk GTD

Combination chemotherapy

MAC

EMA/CO
etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine

EMA/EP

70% remission rate

CNS: brain irradiation, intrathecal methotrexate

Liver: resection to manage complications

Subsequent Pregnancy Outcome

<table>
<thead>
<tr>
<th>Prior Molar pregnancy</th>
<th>Complete</th>
<th>Partial</th>
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<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>
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Garner, Contemp Obstet Gynecol 2001

Pregnancy after Repeat Mole

| Total pregnancies | 34 |
| Total deliveries  | 19 |
| Term             | 55.9% |
| Stillbirth       | 2.9%  |
| Spontaneous abortion | 8.8% |
| Elective abortion | 8.8% |
| Ectopic          | 2.9%  |
| Repeat Mole      | 20.6% |

Garner, Contemp Obstet Gynecol 2001

Pregnancy < 1 year follow-up

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<th>Retrospective review 1966-1996</th>
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<tr>
<td>N=22</td>
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<tr>
<td>Pregnancy within 1 year of receiving chemotherapy</td>
</tr>
<tr>
<td>9 Term delivery, 1 Preterm delivery, 1 IUFD, 4 Spontaneous Ab, 1 Repeat mole</td>
</tr>
<tr>
<td>Time from chemo to conception</td>
</tr>
<tr>
<td>Term pregnancy: 9.8 months</td>
</tr>
<tr>
<td>Pregnancy losses: 6.5 months p&lt;0.05</td>
</tr>
<tr>
<td>27% fetal loss, 4.5% GTD</td>
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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 typically responds well to chemotherapy, even with advanced stage disease.

Patients with GTD can generally expect a normal subsequent pregnancy, but should be monitored for possible recurrence.