Current Management of Gestational Trofoblastic Diseases (GTD)

X. International Turkish – German Gynecology Congress
April 30th and May 4th, 2014, Antalya
TAJEV (Turkish - German Gynecological Education and Research Foundation)

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GTD

- Hydatidiform mole (HM) (complete and partial)
- Gestational trophoblastic neoplasia (GTN)
  - Invasive mole
  - Choriocarcinoma
  - Placental site trophoblastic tumor
  - Epithelioid trophoblastic tumor
Etiologic risk factors - HM

- Advanced or very young maternal age
- Prior HM
- Familial biparental complete HM associated with NLRP7 gene
Morphologic and cytogenetic criteria, CHM

- Uniform hydatid enlargement of villi, absence of fetus or embryo, hyperplastic trophoblast with varying degrees of atypia, absent villous capillaries
- 90% of CHM are 46, XX, originating from duplication of the chromosomes of a haploid sperm
- 10% of CHM are 46, XY, or 46, XX, as a result of fertilization of an empty ovum by 2 sperm (dispermy)
Morphologic and cytogenetic criteria partial HM

- Identifiable fetal or embryonic tissue, chorionic villi with focal edema, functioning villous circulation, focal trophoblastic hyperplasia with mild atypia only

- Most partial moles
  Have a triploid karyotype (usually 69, XXY), resulting from the fertilization of an apparently normal ovum by 2 sperm
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Vaginal bleeding</td>
<td>97%</td>
<td>84%</td>
</tr>
<tr>
<td>Anemia (Hb &lt; 10.0 g/dl)</td>
<td>54%</td>
<td>5%</td>
</tr>
<tr>
<td>Uterine size &gt; dates</td>
<td>51%</td>
<td>28%</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>27%</td>
<td>1%</td>
</tr>
<tr>
<td>Hyperemesis</td>
<td>26%</td>
<td>8%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>2%</td>
<td>0%</td>
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</tbody>
</table>
90% of patients with partial HM have symptoms of incomplete or missed abortion, and the diagnosis is usually made after histologic review of curettage specimens.

The main presenting symptom is vaginal bleeding in 75% of patients.

Other symptoms are infrequent.

Preevacuation hCG levels are >100,000 mIU/mL in <10% of patients.


US plays a critical role in the diagnosis of both complete and partial HM

- Because the chorionic villi of complete HM exhibit diffuse hydropic swelling, vesicular US pattern can be observed, consisting of multiples echoes (holes) within the placental mass and usually no fetus

US facilitate the early diagnosis of a partial HM by demonstrating focal cystic spaces within the placenta and an increase in the transverse diameter of the gestational sac

HCG

- HCG is a disease-specific tumor marker produced by HM and GTN
- HCG levels have been shown to correlate with the burden of disease

False-positive hCG (phantom hCG)

- Some assays may yield false-positive hCG results, with levels as high as 800 mIU/mL, have led to treatment of healthy patients with unnecessary surgery and chemotherapy.

- These antibodies are found in 3-4% of healthy people and can mimic hCG immunoreactivity.

False-positive hCG (phantom hCG)

- There are 3 ways to determine whether hCG assays are falsely positive
  - Determine a urine hCG level, which should be negative
  - Request serial dilution of the serum, which should not show a parallel decrease with dilution
  - Send the serum and urine of the patient to an hCG reference laboratory

- Additionally, there is some cross-reactivity of hCG with LH, which may lead to falsely elevated low levels of hCG. Measurement of LH to identify this possibility and suppression of LH with COC pills will prevent this problem

Quiescent GTD

- Inactive form of GTN that is characterized by persistent, unchanging low levels (<200 mIU/mL) of “real” hCG for at least 3 months associated with a history of GTD or spontaneous abortion, but without clinically detectable disease
- The hCG levels do not change with chemotherapy or surgery
- No hyperglycosylated hCG
- Follow-up of patients with quiescent GTD reveals subsequent development of active GTN in about one-quarter, which is heralded by an increase in both hyperglycosylated hCG and total hCG

False-positive hCG resulting from heterophile antibodies or LH interference should be excluded.

The patient should be thoroughly investigated for evidence of disease, immediate chemotherapy or surgery should be avoided.

The patient should be monitored long term with periodic hCG testing while avoiding pregnancy.

Treatment should be undertaken only when there is a sustained rise in hCG or the appearance of overt clinical disease.

Pathologic diagnosis

- Pathologic diagnosis of CHM and PHM is made by examination of curettage specimens.
- IH staining for p57 (a paternally imprinted, maternally expressed gene) can differentiate absent immunostaining CHM from positively staining hydropic abortuses and PHM.
- Flow cytometry can distinguish diploid CHM from triploid PHM.

References:
Additionally, pathologic diagnosis of invasive mole, choriocarcinoma, PSTT, and ETT can sometimes be made by curettage, biopsy of metastatic lesions, or examination of hysterectomy specimens or placentas.

Biopsy of a vaginal lesion suggestive of a GTN is dangerous because of the massive bleeding that may occur.

Suction evacuation (SE) is the preferred method of evacuation of a HM

IV oxytocin infusion be started at the onset of SE and continued for several hours postop to enhance uterine contractability

SE should be followed by gentle sharp curettage

At least 2 U of blood should be available

Patients who are Rh negative should receive Rh immune globulin at the time of evacuation, as Rh D factor is expressed on trophoblastic cells
Hysterectomy provides permanent sterilization and eliminates the risk of local myometrial invasion as a cause of persistent disease.

Because of the potential for metastatic disease even after hysterectomy, the risk of postmolar GTN still remains at 3-5%, thereby requiring continued hCG follow-up.

Follow-up after molar evacuation

- Trophoblastic sequelae (invasive mole or choriocarcinoma), which develop in approximately 15-20% with complete mole and 1-5% with partial mole

Follow-up after molar evacuation

- Clinical + hCG
- Every week until 3 consecutive tests show normal levels
- After which hCG levels should be determined at 3-month intervals for 6 months after the spontaneous return to normal
- Contraception is recommended for 6 months after the first normal hCG result
- The use of COC pills is preferable

Diagnose of postmolar GTN

- Include at least 1 of the following
  - HCG plateau for 4 consecutive values over 3 weeks
  - HCG rise of $\geq 10\%$ for 3 values over 2 weeks
  - HCG persistence 6 months after molar evacuation
  - Histopathologic diagnosis of CoCa
  - Presence of metastatic disease
  - The FIGO stage is designated by a Roman numeral followed by the modified WHO score designated by an Arabic numeral, separated by a colon
- PSTTs and ETTs are classified separately
Varied presentation depending on the antecedent pregnancy event, extent of disease, histopathology

Postmolar GTN (invasive mole or CoCa) mostly presents as irregular bleeding after evacuation of HM

Signs suggestive of postmolar GTN are an enlarged, irregular uterus and persistent bilateral ovarian enlargement

Occasionally, a metastatic vaginal lesion may be noted on evacuation, disruption of which may cause uncontrolled bleeding

CoCa associated with nonmolar gestation has no characteristic symptoms or signs, which are mostly related to invasion of tumor in the uterus or at metastatic sites
Metastatic workup and an evaluation for risk factors

Complete history and physical examination

Blood cell count, coagulation studies, serum chemistries, blood type and antibody screen, and hCG level

Chest x-ray, if the chest x-ray is negative, CT scans of the abdomen and pelvis, and CT scan or magnetic resonance imaging of the brain

HCG in cerebrospinal fluid may be helpful in detecting brain involvement
Stage

I. Disease confined to uterus

II. Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)

III. Disease extends to lungs with or without genital tract involvement

IV. Disease involves other metastatic sites
## Modified WHO prognostic scoring system as adapted by FIGO

<table>
<thead>
<tr>
<th>Scores</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
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<tbody>
<tr>
<td>Age</td>
<td>&lt; 40</td>
<td>&gt; 40</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>Interval months from index pregnancy</td>
<td>&lt; 4</td>
<td>4–7</td>
<td>7–13</td>
<td>&gt; 13</td>
</tr>
<tr>
<td>Pretreatment serum hCG (IU/L)</td>
<td>&lt; 1000</td>
<td>&lt; 10,000</td>
<td>&lt; 100,000</td>
<td>&gt; 100,000</td>
</tr>
<tr>
<td>Largest tumor size (including uterus)</td>
<td>–</td>
<td>3–&lt; 5 cm</td>
<td>&gt; 5 cm</td>
<td></td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen/kidney</td>
<td>GI</td>
<td>Liver/brain</td>
</tr>
<tr>
<td>Number 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>Single drug</td>
<td>2 or more drugs</td>
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Patients with nonmetastatic (stage I) and low-risk metastatic (stages II and III, score <7) GTN can be treated with single-agent chemotherapy, with resulting survival rates approaching 100%.

Patients classified as having high-risk metastatic disease (stage IV and stages II-III, score ≥7) should be treated with multiagent chemotherapy ± adjuvant radiation or surgery to achieve cure rates of 80-90%.
Chemotherapy for low-risk gestational trophoblastic neoplasia

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Remission rate, %</th>
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<tbody>
<tr>
<td>1. MTX 0.4 mg/kg (maximum 25 mg)/d IV or IM for 5 d; repeat every 14 d</td>
<td>87–93</td>
</tr>
<tr>
<td>2. MTX 30-50 mg/m² IM weekly</td>
<td>49–74</td>
</tr>
<tr>
<td>3. MTX 1 mg/kg IM d 1, 3, 5, 7; folinic acid 0.1 mg/kg IM d 2, 4, 6, 8; repeat every</td>
<td>74–90</td>
</tr>
<tr>
<td>15-18 d, or as needed</td>
<td></td>
</tr>
<tr>
<td>4. MTX 100 mg/m² IVP, then 200 mg/m² in 500 mL D5W over 12 h; folinic acid 15 mg IM</td>
<td>69–90</td>
</tr>
<tr>
<td>or PO q 12 h for 4 doses beginning 24 h after start of MTX; repeat every 18 d, or</td>
<td></td>
</tr>
<tr>
<td>as needed</td>
<td></td>
</tr>
<tr>
<td>5. Act-D 10-13 μg/kg IV qd for 5 d; repeat every 14 d</td>
<td>77–94</td>
</tr>
<tr>
<td>6. Act-D 1.25 mg/m² IV every 2 wk</td>
<td>69–90</td>
</tr>
<tr>
<td>7. Alternating MTX/Act-D regimens 1 and 5</td>
<td>100</td>
</tr>
</tbody>
</table>

Hysterectomy for low-risk GTN may be performed as adjuvant treatment with the initiation of chemotherapy to shorten the duration of treatment if fertility preservation is not desired.

Hysterectomy may also become necessary to eradicate persistent, chemotherapy-resistant disease in the uterus or to remedy uterine hemorrhage from tumor.

Hysterectomy is the treatment of choice for PSTT and ETT.
High-risk metastatic disease

- Treated initially with multiagent chemotherapy with or without adjuvant surgery or radiation therapy
- EMA-CO is the initial treatment of choice for high-risk metastatic GTN
In 2 reported series, the complete response rates were 71% and 67%, and the overall survival rates were 91% and 93%, respectively.

The only patients who died had FIGO stage IV disease with scores >12


High-risk metastatic disease who failed primary therapy with EMA-CO

- Of the 10 patients who failed primary therapy with EMA-CO, 9 (90%) had complete clinical responses to EMA-EP or bleomycin, etoposide, cisplatin, but only 6 (60%) subsequently achieved a lasting remission

The overall cure rate in treating these tumors is currently >90%.

Nonmetastatic (stage I) and low-risk metastatic (stages II and III, score <7) GTN can be treated with single-agent chemotherapy resulting in a survival rate approaching 100%.

High-risk GTN (stages II-IV, score ≥7) requires initial multiagent chemotherapy with or without adjuvant radiation and surgery to achieve a survival rate of 80-90%.
- Centralisation of care is necessary
- Treatment of HM is suction D&C
- Anti-D prophylaxis is recommended following suction D&C
- The FIGO scoring system should be used to determine the risk of GTN becoming resistant to single-agent chemotherapy
- Patients with a FIGO score of 0–6 and / or stage I-III can be treated with either single-agent MTX or ActD
Patients with a FIGO score of ≥7 or stage IV should receive multi-agent chemotherapy EMA/CO.

High-risk failures can be frequently salvaged with further chemotherapy with EP/EMA or TE/TP.

Surgery alone can effectively salvage some patients with isolated foci of chemoresistant disease.

Cure for low and high risk disease is 100% and 80-90% respectively.
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High-risk metastatic disease

![Diagram showing the process of a partial mole formation](image)

**PARTIAL MOLE**
- 23X
- 23Y
- One or two sperm
- 46XY

Egg

- 23X
- 23X
- 23Y

Maternal and paternal chromosomes (Triploid)

- 69XXY
- 69XXX