بحم الله الرحمن الرحيم
GESTATIONAL TROPHOBLASTIC DISEASE

Prepared by: Dr. Noor Muqdad
Classification of gestational trophoblastic disease

- **BENIGN:** complete and partial H. mole
- **MALIGNANT:**
  1. Invasive mole
  2. Placental site trophoblastic tumor
  3. Choriocarcinoma
INTRODUCTION

The majority of patients \{80–90\} with GTD follow a benign course with their remitting spontaneously.

Most patients with metastatic disease can be effectively cured with chemotherapy.
INTRODUCTION

This diverse group of diseases has a sensitive tumor marker, β- hCG, which is secreted by all of these tumors and allow accurate follow up and assessment of the disease.
ETIOLOGY

- Although the cause of GTD is unknown, it is known to occur more frequently in women younger than 20 years and in those older than 40 years.
- May result from defective fertilization.
- The incidence of molar pregnancy has been noted to be higher in geographic area where people consume less β-carotene and folic acid.
HYDATIDIFORM MOLE

- Incidence of complete and partial mole was found 1/1945 and 1/695 pregnancies

- Complete mole
  - Low intake of carotene, vitamin A deficiency
  - Maternal age >35 years

- Partial mole
  - The use of oral contraception
  - History of irregular menstruation
H.MOLE

The risk of development of a second molar pregnancy is {1%–3%} or as much as 40 times greater than the risk of developing the first molar pregnancy.
COMPLETE H.MOLE

- The karyotype
  - Usually 46XX
  - About 10% have 46XY
- The molar chromosome are entirely paternal origin
Normal Pregnancy Male

Egg with 23X

Fertilization

Sperm with 23Y

Fertilized Zygote 46XY

Normal Pregnancy Female

Egg with 23X

Fertilization

Sperm with 23X

Fertilized Zygote 46XX
Complete Mole Pregnancy Male

Empty Egg → Penetration → Sperm with 23X → Egg with 23X → Fertilization → Second Sperm with 23Y → Fertilized molar Zygote 46XY

Complete Mole Pregnancy Female

Empty Egg → Penetration → Sperm with 23X → Egg with 23X → Fertilization → Second Sperm with 23X → Fertilized molar Zygote 46XX
PATHOLOGIC CHARACTERISTIC
GROSSLY There is vesicles which look like bunch of grapes. With out fetus and this may represent a form of twinning
NORMAL PREGNANCY showing smaller villi
PATHOLOGICAL CHARACTERISTIC
Complete mole showing large villi with stromal edema, absence of fetal blood vessels and marked trophoblastic proliferation.
PARTIAL H.MOLE

- The karyotype
  - Triploid
  karyotype \{69\text{chromosome}\}
  - The extra haploid chromosome derived from father
    - 69XXX, 69XXY, 69XYY
Partial mole with attached fetus. The fetus showed no abnormality and was connected to the mole by a normal umbilical cord.
PATHOLOGICAL CHARACTERISTIC

In partial moles, some villi appear normal, whereas others are swollen, avascular, and grape-like (though not as large as a complete mole). There is minimal trophoblastic proliferation. In fact, most placentas in cases of triploid
PATHOLOGICAL CHARACTERISTIC
<table>
<thead>
<tr>
<th>Features</th>
<th>complete</th>
<th>partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic tissue</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Swelling of C.V.</td>
<td>diffuse</td>
<td>focal</td>
</tr>
<tr>
<td>Trophoblastic H.</td>
<td>diffuse</td>
<td>focal</td>
</tr>
<tr>
<td>Scalloping of C.V.</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Trophoblastic stromal inclusion</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Karyotype</td>
<td>46XX,46XY</td>
<td>triploid</td>
</tr>
</tbody>
</table>
Complete mole:
- Vaginal bleeding {84%}
- Excessive uterine size {28%}
- Preeclampsia {27%} and hyperemesis gravidarum {8%}
- Hyperthyroidism {7%}
- Trophoblastic embolism {2%}
- Theca lutein ovarian cysts
  * prominent cyst {6 cm. in diameter}
CLINICAL PRESENTATION

*Result from high serum h.C.G. and this cause ovarian hyper stimulation
*After molar evacuation, cyst normally regress spontaneously with in {2–4 mon}
*cyst may cause symptom of marked pelvic pressure→ decompressed by aspirate
CLINICAL PRESENTATION

Partial mole:

- The patients have sign and symptom of incomplete or missed abortion
- The main initial sign was vaginal bleeding
- Can be diagnosed after histological review of tissue by curettage
INVESTIGATION

*Complete mole:
  - Ultrasound is reliable and sensitive $\rightarrow$ vesicular ultrasonographic pattern
  - Chorionic villi diffuse hydropic swelling
Investigation

Partial mole:
- Focal cystic spaces in the placental site tissue
- Increase in the transverse diameter of the gestational sac
Figure 9. Partial hydatidiform mole. Thick, irregular trophoblast, with sonographic signs suggesting anembryonic gestation. Histopathological study demonstrated the presence of molar tissue in the evacuation material.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disease confined to uterus</td>
</tr>
<tr>
<td>I a</td>
<td>Disease confined to uterus + no risk factor</td>
</tr>
<tr>
<td>I b</td>
<td>Disease confined to uterus + 1 risk factor</td>
</tr>
<tr>
<td>I c</td>
<td>Disease confined to uterus + 2 risk factor</td>
</tr>
<tr>
<td>II</td>
<td>GTT extending out side uterus but limited to genital structures {adnexa, vagina, broad ligament}</td>
</tr>
<tr>
<td>II a</td>
<td>GTT involving genital structures + no risk factor</td>
</tr>
<tr>
<td>II b</td>
<td>GTT extending out side uterus but limited to genital structures + 1 risk factor</td>
</tr>
<tr>
<td>II c</td>
<td>GTT extending out side uterus but limited to genital structures + 2 risk factor</td>
</tr>
<tr>
<td>Stage</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Stage III</td>
<td>GTD extending to lungs with or without known genital tract involvement</td>
</tr>
<tr>
<td>Stage III a</td>
<td>GTT extending to lungs with or without known genital tract involvement</td>
</tr>
<tr>
<td></td>
<td>No risk factor</td>
</tr>
<tr>
<td>Stage III b</td>
<td>GTT extending to lungs with or without known genital tract involvement</td>
</tr>
<tr>
<td></td>
<td>1 risk factor</td>
</tr>
<tr>
<td>Stage III c</td>
<td>GTT extending to lungs with or without known genital tract involvement</td>
</tr>
<tr>
<td></td>
<td>2 risk factor</td>
</tr>
<tr>
<td>Stage VI</td>
<td>All other metastatic sites</td>
</tr>
<tr>
<td>Stage VI a</td>
<td>All other metastatic sites S + no risk factor</td>
</tr>
<tr>
<td>Stage VI b</td>
<td>All other metastatic sites S + 1 risk factor</td>
</tr>
<tr>
<td>Stage VI c</td>
<td>All other metastatic sites S + 2 risk factor</td>
</tr>
</tbody>
</table>
Risk factor affecting staging

- $hCG > 100,000 \text{ IU/ML}$
- Duration of disease $>6$ month from termination of antecedent pregnancy
Treatment

- Suction evacuation: it is standard therapy followed by sharp curettage, regardless of the duration of pregnancy
Treatment

- Hysterectomy: does not prevent metastasis so the patient require follow-up hCG level
Treatment

• Prophylactic chemotherapy:
  #The use of prophylactic chemotherapy is controversial since 90% of these individuals have spontaneous remission
  #Chemotherapy should be initiated if $\beta - hCG$ levels plateau or rise at any time
Follow – up

hCG level : after molar evacuation

* Monitored weekly until normal for 3 wk.
* Follow by monthly until normal for 6 mon.
* The average time to achieve first normal hCG level is about 9 week
* contraception: during the entire interval of hCG follow – up
Persistent
gestational
trophoblastic tumor

Non metastatic

Metastatic
Non metastatic disease

- Locally invasive GTT develop in about 15%

- Patient usually present with irregular vaginal bleeding, theca lutein cysts, uterine subinvolution or asymptomatic enlargement, persistently elevated serum hCG level
Risk factor

• After molar $\rightarrow$ H.mole $\rightarrow$ choriocarcinoma

• After non molar $\rightarrow$ always choriocarcinoma
Invasive mole

- Invasive mole is usually a locally invasive tumor
- It constitutes about 5%–10% of all molar pregnancies
- Represent the majority of those with persistent β hCG levels after molar evacuation
Placental – site trophoblastic tumor

- Uncommon but important variant of choriocarcinoma
- Characteristic: *produce small amount of hCG and hPL
  * remain confined to the uterus
  * metastasizing late in their course
- Relatively insensitive to chemotherapy
Metastatic disease

• Metastatic GTT occur in about 4% after complete mole
• Symptom of metastasis may result from spontaneous bleeding at metastatic foci
Choriocarcinoma

• It is frankly malignant form of GTT
• About ½ of patients with gestational choriocarcinoma have had a preceding molar pregnancy
• In remaining patients the disease is preceded by spontaneous or induced abortion, ectopic pregnancy or normal pregnancy
Choriocarcinoma

- Trophoblastic disease following a normal pregnancy is always Choriocarcinoma
- The tumor has a tendency to disseminate hematogenously particularly to the lungs, vagina, brain, liver, kidneys and GIT
Common site of metastasis

80%
4 principal pulmonary pattern

- Snow storm or alveolar pattern
- Discrete rounded densities
- Pleural effusion
- Embolic pattern
Investigation

- If $\beta$ hCG level is elevated, the workup is the same as that for patients with H.mole
  - C.T $\rightarrow$ abdomen
    $\rightarrow$ pelvis
    $\rightarrow$ head
- L.P.
# Prognostic scoring system

: WHO

<table>
<thead>
<tr>
<th></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>H.mole</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval (preg.→CMT)</td>
<td>&lt;4</td>
<td>4–6</td>
<td>7–12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>mon.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG</td>
<td>&lt;1000</td>
<td>1000–10000</td>
<td>10000–100000</td>
<td>&gt;100000</td>
</tr>
<tr>
<td>ABO blood group</td>
<td>O,A</td>
<td>B,AB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Prognostic scoring system: WHO

<table>
<thead>
<tr>
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<th>0</th>
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<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Largest tumor + uterine (cm.)</td>
<td>&lt;3</td>
<td>3–5</td>
<td>&gt;5</td>
<td></td>
</tr>
<tr>
<td>Site of metastases</td>
<td></td>
<td>Spleen, kidney</td>
<td>G.I.T., Liver</td>
<td>brain</td>
</tr>
<tr>
<td>NO. of metastases</td>
<td>1–3</td>
<td>4–8</td>
<td>&gt;8</td>
<td></td>
</tr>
<tr>
<td>Prior CMT</td>
<td></td>
<td>1 drug</td>
<td>&gt;2 drug</td>
<td></td>
</tr>
</tbody>
</table>
Prognostic scoring system

: WHO

- Total score
  - Low risk <4
  - Middle risk 5–7
  - High risk >8

*Categorized

  - Stage 1 → usually low-risk score
  - Stage 4 → high-risk score

Prognostic scoring system applied mainly to patient with stage 2 and 3
DX.

• history
• Examination
• Investigation : – hCG
  – Liver function test
  – thyroid function test
  – renal function test
  – W.B.C and platelet
  – C.X.R. , C. T. chest
  – C.T. , M.R.I. brain
  – U / S or C.T. abdomen and pelvis
## Protocol for treatment

### GTT

<table>
<thead>
<tr>
<th>Stage 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>Single CMT or adj hysterectomy + CMT</td>
</tr>
<tr>
<td>Resistant</td>
<td>CMT {Combination} , hysterectomy + Adj CMT , Local resection , pelvic infusion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2 +3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk → Initial</td>
<td>Single CMT</td>
</tr>
</tbody>
</table>
# Protocol for treatment

## GTT

| Stage 2 and 3 | | | |
|---------------|--------------------------|
| low risk → resistant | Combination CMT | Combination CMT |
| high risk → initial | Second – line combination CMT |
| ↓ | | |
| resistant | | |

| Stage 4 | | | |
|----------|--------------------------|
| Initial | Combination CMT |
| Brain | Whole – heat irradiation {3000 cGy} |
| Liver resistant | Resection |
| | Combination CMT |
| | Hepatic arterial infusion |
Follow – up

Stage 1 – 3 receive follow – up with;

• Weekly hCG level until normal for 3 wk
• Monthly hCG level until normal for 12 mon.

• Effective contraception during the entire interval of hormonal follow – up
Follow – up

Stage 4 receive follow up with;

• Weekly hCG level until normal for 3 week

• Monthly hCG level until normal for 24 month
CHEMOTHERAPY

• Single – agent treatment
  – Actinomycin D {Act – D}
  – Methotrexate {MTX}
  – Methotrexate with folinic acid {MTX – FA}

• Given every other week as 5 – day regimen or pulsatile weekly
CHEMOTHERAPY

- Technique of single – agent treatment:
  - hCG measure weekly after each course of CMT
- After the 1st treatment: 1–further CMT is withheld as long as hCG level is falling progressively
  2–Additional single – agent CMT is not administered
CHEMOTHERAPY

• 2\textsuperscript{nd} course administered under following condition:
  – hCG level plateaus more than 3 week or begin to rise
  – If hCG not decline by 1 log within 18 day after complete 1\textsuperscript{st} treatment

• If inadequate response to 2\textsuperscript{nd} course of MTX–FA → the patient consider to be resistant
CHEMOTHERAPY

- Combination chemotherapy
- Triple therapy: MTX, Act-D, cyclophosphamide
- EMA–CO: etoposide, MTX, Act-D, cyclophosphamide, vincristine
- EMA–EP: etoposide and cisplatine on day 8
- Duration of therapy
  until 3 normal hCG level
  After that, at least 2 additional courses are administered
Subsequent pregnancies

- After H.mole
  - after one molar pregnancy risk of having molar in the future gestation is about 1%
  - for any subsequent pregnancy perform pelvic ultrasound in 1st trimester, and hCG measurement 6 wk after complete of pregnancy
Subsequent pregnancies

- After persistant GTT the frequency of congenital anomalies is not increase although CMT have teratogenic effect
THANK you