GTD (gestational trophoblastic disease)

PART ONE
Learning objectives:

- To clarify the definition, aetiology, risk factors and the classification of GTN
- Genetics of H. Mole
- Diagnosis of GTN
- Principles of management of both benign and malignant varieties

References:
1. Essentials of obstetrics and gynecology by Hacker and Moore
2. Gynecology by Ten Teachers 19th ed
GTD

(gestational trophoblastic disease)

It is a spectrum of diseases arises from abnormal fertilization event leading to an abnormal pregnancy
CLASSIFICATION:

1- Benign hydatidiform mole which further subdivided into partial and complete mole.
2- Invasive mole (chorioadenoma destruens) which can metastasize.
3- Choriocarcinoma (frankly malignant).
4- Placental site trophoblastic tumour (PSTT).
GTD

The majority of the patients follow a benign course and their disease remitting spontaneously.
The disease is characterized by the sensitive tumour marker (β-hCG) which is secreted by the tumour cells and allows accurate diagnosis and follow up of the disease.
Etiology, risk factors and epidemiology

The incidence of this disease is varying according to many factors:

- The incidence of GTD varies between 0.5 and 8.3 cases per 1000 live births.
- UK figure is approximately 1.5 per 1000 births, in contrast, the incidence is approximately twice as high in some Asian countries.
- It is higher with maternal age <16 (1.3 folds) and ≥45 years (10 folds).
- The risk of recurrence i.e. developing 2nd molar pregnancy is 2% or higher, and 15-20% following 2 moles and 50% following 3 moles.
Etiology and epidemiology

- Blood group A woman if married to a man with blood group O (there is 10 folds higher risk of choriocarcinoma), and if the woman of bl.gp AB it carries a relatively worse prognosis.

- Diet may play a role: low dietary intake of carotene, low protein, animal fat and folic acid intake predispose to GTN

- Low estrogen status?
pathology

It is a spectrum of diseases arises from abnormal fertilization event leading to an abnormal pregnancy
Genetics of H. mole

A. Complete mole
- 23X
- Chromosome duplication
- 46XX
- Empty ovum
- Homozygous complete mole

B. Complete mole
- 23X or Y
- Dispermy
- Empty ovum
- 46XX
- 46XY
- Heterozygous complete mole

C. Partial mole
- 23X or Y
- 23X or Y
- Dispermy
- 23X
- Ovum
- 69XXX
- 69XXY
- Triploid partial mole
- 69XYY
- Rare
Complete molar pregnancy

1- It is abnormal pregnancy
2- Characterized by multiple grape-like vesicles filling and distending the uterine cavity sometimes it develop in the tubes or the ovary,
3- The fetus and the amnion are absent.
4- And carry 20-30% risk of persistent disease.
Histologically (molar pregnancy):

1- Hydropic villi.
2- Absence of blood vessels.
3- hyperplasia of trophoblastic epithelium.
Partial mole:

The partial mole (69 XXY or XYY)

1- The fetus is present and died in the 8-9 weeks (aneuploidy),
2- Focal trophoblastic hyperplasia at the implantation site,
3- The villi are present
4- Risk of persistent disease is <0.5%
# Pathological features of hydatidiform mole

<table>
<thead>
<tr>
<th></th>
<th>Complete</th>
<th>Partial</th>
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<tbody>
<tr>
<td><strong>Macroscopic</strong></td>
<td>Often recognizable, with characteristic grape-like structures</td>
<td>Can resemble hydropic abortion; may have recognizable fetal tissues</td>
</tr>
<tr>
<td><strong>Microscopic</strong></td>
<td>Diffusely hydropic villi</td>
<td>Focal hydropic swelling of villi</td>
</tr>
<tr>
<td></td>
<td>Atypical and hyperplastic trophoblast</td>
<td>Focal trophoblastic hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Usually diagnosable from uterine products</td>
<td>Often misdiagnosed as hydropic abortion or complete mole</td>
</tr>
<tr>
<td><strong>Karyotype</strong></td>
<td>Usually diploid (paternally derived)</td>
<td>Usually triploid (maternal contribution)</td>
</tr>
</tbody>
</table>
## Clinical features of hydatidiform mole

<table>
<thead>
<tr>
<th></th>
<th>Complete</th>
<th>Partial</th>
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<tbody>
<tr>
<td><strong>Features</strong></td>
<td>May be severe and/or accompanied by paraneoplastic sequelae</td>
<td>Often mild, resembling spontaneous miscarriage</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Usually suspected on clinical or ultrasound scan findings</td>
<td>Often unsuspected and retrospectively diagnosed after uterine evacuation</td>
</tr>
<tr>
<td><strong>Persisten</strong></td>
<td>In up to 20% of cases</td>
<td>In &lt;0.5% of cases</td>
</tr>
<tr>
<td><strong>trophoblastic disease</strong></td>
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</table>
Invasive mole:

1. It occur in 20% of patients with H.mole,
2. pathologically it is the same as hydatidiform mole but penetrates deeply into the myometrium or the adjacent structures
3. C/F: profuse hge, lower abd pain, hematuria, rectal bleeding, intra peritoneal bleeding, emboli to the lung
4. It may regress spontaneously
Diagnosis of H.Mole:

1) Symptoms and signs:
- Abnormal vaginal bleeding in the 1st and the beginning of the 2nd trimesters in > 90% of the patients.
- Anemia: dilutional or may be due to hemorrhage.
- Large for date uterus with soft (doughy) in consistency
- No fetal parts with negative fetal heart tones
**Symptoms and signs:**

- **Pre eclampsia** early before 20\(^{th}\) week of gestation.
- **Hyperemesis** in 1/3 of the patients.
- **Ovarian cysts**: multiple theca leutin cyst due to high hCG.
- **Hyperthyroidism**: it is mild or subclinical
- **Expulsion of vesicles vaginally**
hCG
2) **Investigations**

1. **(β-hCG):**
   It is higher than normal pregnancy values and can be detected in the serum or urine of all patients (its level correlate closely with the number of viable tumour cells). (>200 000 U/L)

2. **U/S it is the diagnostic method of choice (snow storm appearance)**

3. **CXR to show metastatic disease**
Differential diagnosis

1- ?
2- ?
3- ?
4- ?
Treatment:

- Evacuation of the uterus preceded by B hCG level, complete blood count, renal function test, liver function test, coagulation profile, ECG and chest X-ray.
- Blood loss is moderate **SO** (prepare blood)
The **GOLD standard** for termination of pregnancy is by **suction curettage** which is safe, rapid and effective method. When the conceptus nearly totally evacuated we start the oxytocin to induce uterine contractions and avoid perforation.
Hysterectomy is done in certain situations:
1- the woman >35 years completed family
2- high risk of persistent GTN may be lowered by hysterectomy from 20% to 3.5% only.

Medical induction is not recommended because fear of showering emboli through the blood stream.

Hysterotomy is not recommended.

All Rh negative women should receive anti-D immunoglobulin
Complications

1. perforation
2. hemorrhage
3. Deportation of trophoblastic tissues to the lungs is frequent which may regress spontaneously but sometime postevacuation acute pulmonary insufficiency may result leading to dyspnoea, and cyanosis 4-6 hours after evacuation.
4. Pulmonary edema from high output heart failure, pre eclampsia, anemia, and hyperthyroidism.
5. Sepsis.
**Surveillance following molar pregnancy**

- Following evacuation (β-hCG) titers should be estimated serially because of the 20-30% risk of persistent disease.
- The determination should be started 48 hours after the evacuation and weekly until it becomes undetectable (< 5mIU).
- Effective contraceptive measures is essential.
The titer remission should occur spontaneously by 12 - 14 weeks then the patient should be followed up monthly for 6-12 months before the patient is released from close medical supervision.
• Gynecological examination 1 week after evacuation for uterine size, adnexial mass, vulval and vaginal deposits (metastasis). And should be repeated during the period of surveillance.

• 1 year after negative titers pregnancy is allowed and complications are similar to those of the general population
When we give chemotherapy for H.mole after evacuation?

1. -?
2. -?
3. -?
4. -?
5. -?
6. -?
Malignant GTN
Malignant GTN

The malignant GTN can be classified into:

- the non-metastatic: invasive mole
- and the metastatic: choriocarcinoma and the PSTT
Malignant disease can be suspected when

- **1- Plateauing** or rising B-hCG value over a period of 3 consecutive weeks.
- **2- A rise** of B-hCG over a period of 2 weeks.
- **3- Persistence** of a detectable B-hCG after 6 months of evacuation.
The frankly malignant disease is further subdivided into

1. **Good prognosis** group (low risk group)
2. And the **poor prognosis** group (high risk group).
Choriocarcinoma:

The incidence:

- between 1:10 000 to 1:70 000 deliveries in the west.
- And between 1:250 to 1:6000 deliveries in Asia
Choriocarcinoma

The *antece dent pregnancy* is
1- H. mole in 50%,
2- normal pregnancy in 25%
3- abortion or ectopic pregnancy in 25%.
Clinical Presentation

1- Vaginal bleeding is the most common symptom.
2- Lower abdominal pain because of invasion of the surrounding structures.
3- Abdominal AND/OR vaginal mass.
4- Amenorrhea may precede bleeding caused by the high B-hCG produced by the tumor mass.
Clinical Presentation

5- Pulmonary metastasis may cause dyspnoea and haemoptysis it may be misdiagnosed as pulmonary T.B and it can be diagnosed by CXR.

6- Neurological abnormality may indicate brain invasion.

7- High index of suspicion is required to diagnose it especially if it follows normal pregnancy or abortion.

8- it invade the myometrium and metastasizes to the lungs, brain, liver, and other organs.
On examination:

- Most of the patients have *enlarged uterus* as well as ovarian enlargement by *theca lutein cysts*.
- Sites of metastasis should be looked for especially in the vagina cervix and the adnexia
Investigations:

1- B-hCG level in the serum or the urine.  
   it is very high > 100 000 IU / L
2- U/S for the pelvis, liver, kidneys…
3- CXR.
4- CT for the brain, liver, and pelvic organs metastasis.
5- MRI for the brain metastasis.
6- Lumber puncture: CSF to measure the B-hCG level in the CSF it should be greater than 1:40 (the ratio of the level in the CSF to that in the serum)
7- CBP, LFT, RFT, and the coagulation study.
Confirmation of the diagnosis is made by Histopathology of curettage products but curettage carry high risk of uterine perforation and dissemination of the disease, so it can be diagnosed basically depending on the clinical suspicion and high B-hCG levels.
Staging of the disease

FIGO anatomic staging:

- Stage I: disease is confined to the uterus.
- Stage II: disease extends outside the uterus but limited to the genital tract.
- Stage III: disease extends to the lungs with or without genital tract invasion.
- Stage IV: all other metastasis
Classification of the disease according to the prognostic factors:

1- Good prognosis metastatic disease:
2- Poor prognosis metastatic disease:
1- Good prognosis metastatic disease (criteria)

a- short duration (<4 months) between the antecedent pregnancy and chemotherapy.

b- Serum B- hCG <40 000 mIU /ml

c- No metastasis to the brain and the liver.

d- No prior chemotherapy.
2- Poor prognosis metastatic disease (criteria)

a- long duration from the antecedent pregnancy (>4 months) to chemotherapy.
b- Serum B- hCG >40 000 mIU /ml.
c- Metastasis to the brain.
d- Unsuccessful prior chemotherapy.
e- If the disease is following term pregnancy.
Another scoring system is the FIGO scoring:
<table>
<thead>
<tr>
<th>Scores</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;40</td>
<td>≥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>Months from index pregnancy</td>
<td>&lt;4</td>
<td>4–6</td>
<td>7–13</td>
<td>≥13</td>
</tr>
<tr>
<td>Pre-treatment hCG</td>
<td>&lt;1000</td>
<td>1000–10,000</td>
<td>1000–100,000</td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>Largest tumour size</td>
<td>&lt;3 cm</td>
<td>3–5 cm</td>
<td>≥5 cm</td>
<td>–</td>
</tr>
<tr>
<td>Site of mets</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastro-intestinal</td>
<td>Brain, liver</td>
</tr>
<tr>
<td>Number of mets</td>
<td>–</td>
<td>1–4</td>
<td>5–8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td>–</td>
<td>–</td>
<td>Single agent</td>
<td>Two or more drugs</td>
</tr>
</tbody>
</table>
the WHO scoring system which is based on an individual risk factors has two categories:

- low risk
- and high risk categories based on total score:
  - If score 0-6 (low risk)
  - If score of 7 and more (high risk)
Treatment

For the non metastatic GTD:

1- Single agent chemotherapy: either methotrexate (MTX) or actinomycin –D (dactinomycin).

2- Combined chemotherapy with hysterectomy in female who not wish to preserve reproductive function and her disease is confined to the uterus.
<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Methotrexate 50 mg im at noon</td>
</tr>
<tr>
<td>2</td>
<td>Folinic acid 30 mg po at 6 p.m.</td>
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</tr>
<tr>
<td>8</td>
<td>Folinic acid 30 mg po at 6 p.m.</td>
</tr>
</tbody>
</table>
During the treatment cycle or once per week we have to check the RFT, LFT, CBC and platelet count.
Treatment should be **stopped** when:

When the patient’s condition deteriorates:

- WBC < 3000
- PLAT < 100,000
- Elevated liver enzymes
- Or severe side effects: severe stomatitis, GIT ulceration or febrile course.
Switching to alternative chemotherapy when:

When the patient is not responding to this agent like in rising or plateauing titer or when new metastasis appear while the patient on treatment and if the hormone is detectable after 5 courses of chemotherapy which indicate treatment failure.

This will indicate switching to new agent.
*Contraception should be continued for 1 year following remission.

* Chemotherapy is continued for 1 cycle following negative hCG titer.

* The advantage of single agent chemotherapy is less toxic but treatment failure is about 6-10%
follow up program:

- B-hCG weekly until 3 consecutive negative titer, then monthly for a year, then 2 monthly for another year, then 6 monthly for life,

- the follow up need Pelvic examination and CXR together with the hCG titer
Poor prognosis (high risk) metastatic disease group:

- those respond poorly (<40% response rate) to single agent chemotherapy.
- Prior unsuccessful chemotherapy is one of the worst prognostic factors because of considerable toxicity and depleting bone marrow reserves.
Combined chemotherapy for high risk group

- CURRENTLY:
  - EMA-CO:
    This protocol gives the best response rate (80%)
IF RESISTANCE OCCURS

- **Adjuvant surgery**: hysterectomy, thoracotomy or craniotomy for chemotherapy resistant malignant masses.
- **Platinum based** drugs are to be used which give better results of response but with higher side effects.
Example of treatment course

Fig. 15.2 An individual example of the pattern of hCG levels during the course of management.
PSTT

- Derived from intermediate trophoblast
- Local invasion occurs into the myometrium and lymphatics and less commonly into the vasculature,
- It occur with any type of pregnancy or months to years later.
- It is treated by hysterectomy because of resistance to chemotherapy
- If there is metastasis it is an indication for chemotherapy.
1. For H.Mole the prognosis is excellent,
2. and for the non metastatic disease the prognosis is very good.
3. For the good prognostic group the cure rate is 75-85%,
4. and for the poor prognosis group if there is liver metastases the survival from (0-60%).
5. The survival is <20% if previous failed chemotherapy or when metastases to the CNS occur in the 1st few months following termination of chemotherapy.
Secondary tumor induction:

patients with multiple agent chemotherapy especially (Etoposide) have increased risk to develop myeloid leukemia and colonic cancer.
Subsequent pregnancy

- There are no extra complication during pregnancy but require good follow up by U/S and B-hCG levels because of the 2% risk of recurrence after 1 mole and 20% after 2 moles and 50% after 3 moles.

- After delivery placenta should be sent for histopathological study, and B-hCG level must be measured 6 weeks postpartum.
The End

to be continued...

… malignant GTD
hCG levels of normal pregnancy in weeks from LMP (gestational age)

- 3 weeks LMP: 5 – 50 mIU/mL
- 4 weeks LMP: 5 – 426 mIU/mL
- 5 weeks LMP: 18 – 7,340 mIU/mL
- 6 weeks LMP: 1,080 – 56,500 mIU/mL
- 7 – 8 weeks LMP: 7, 650 – 229,000 mIU/mL
- 9 – 12 weeks LMP: 25,700 – 288,000 mIU/mL
- 13 – 16 weeks LMP: 13,300 – 254,000 mIU/mL
- 17 – 24 weeks LMP: 4,060 – 165,400 mIU/mL
- 25 – 40 weeks LMP: 3,640 – 117,000 mIU/mL
- Non-pregnant females: 0 – 5 mIU/mL
- Postmenopausal females: 0 – 8 mIU/mL