Reviewed By
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Video Case

Gest. Trophoblastic Tumors

Objectives:

- ➔ Describe the symptoms and physical examination findings of a patient with GTN including molar pregnancy.
- ➔ Describe the diagnostic methods, treatment options and follow-up for GTN including molar pregnancy.
- ➔ Recognize the difference between molar pregnancy and malignant GTN.

This is based on 437 video case and 438+439 notes, If you want the original Slides of 438 please click here

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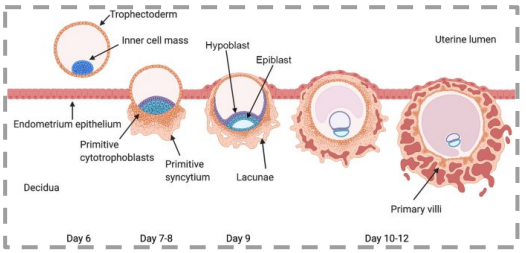
Female presentation

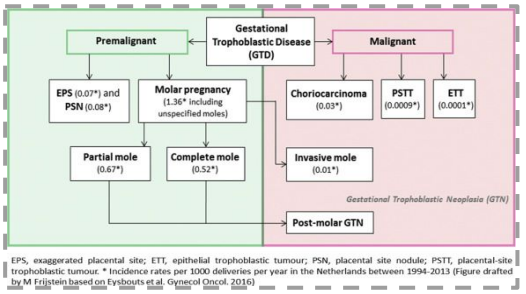
Video Case | Editing File

Gestational Trophoblastic Diseases / GTD

It's **an abnormal proliferation of trophoblasts** (cytotrophoblast and/or syncytiotrophoblast) from the placenta. It includes :

- Benign / **Hydatidiform moles / molar pregnancy**
- **Malignant / Gestational trophoblastic neoplasia**





How to differentiate between them ?
The invasion of myometrium ⟶ malignant.

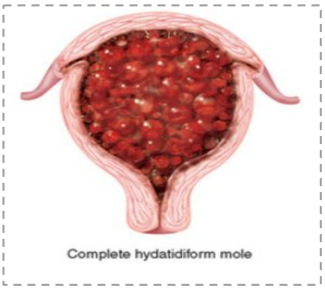
Risk factors :

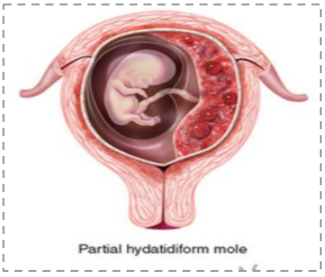
1. Previous GTD.
2. Maternal age: upper and lower extremes.
3. mutation in the NLRP7 gene.
4. Ethnicity: higher incidence in Asian, native American, or African ancestry (Very common in Saudi Arabia).
5. Dietary factors: less β-carotene (a retinoid / vitamin A) and folic acid.

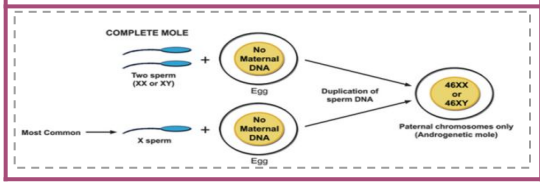
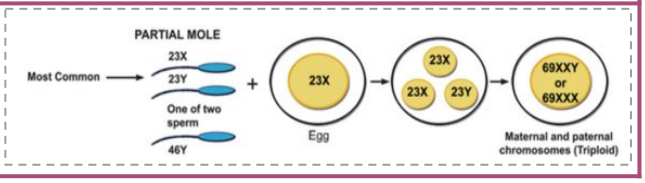
- NOTE : Molar pregnancy and spontaneous abortion will increase risk for GTN

Molar pregnancy :

are non-invasive, localized, tumors that result from **abnormal fertilization events** that result in proliferation of trophoblastic tissues. It includes :


Complete hydatidiform mole

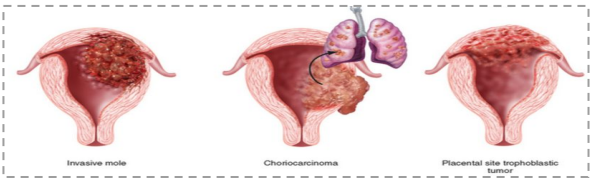

Partial hydatidiform mole

Complete mole	Incomplete (partial) mole
Fertilization of an **empty ovum** with two sperms or one sperm that will divide later	Fertilization of a **normal ovum (haploid)** with two sperms or one sperm that will divide later (⅓ maternal and ⅔ paternal)
Is a tumor of **syncytiotrophoblast**	Is a tumor of **cytotrophoblast**
Most common genetic **46XX** , Only a small percentage of lesions are 46XY	Most common generic **69XXY**, The majority of the remaining lesions are 69,XXX or 69,XYY
No fetal components	Fetal components present
histopathologic findings : 1) Diffuse **hydropic villi** 2) Hyperplasia of trophoblastic tissue 3) Absence of fetal blood vessel	histopathologic findings : 1) Partial **hydropic villi** 2) Less striking trophoblastic hyperplasia 3) Fetal blood vessel are seen.
6-32% risk of malignancy	<5% risk of malignancy
	

Gestational Trophoblastic Neoplasia (GTN):

It's a malignant form of GTD,

- These may follow a normal pregnancy or molar pregnancy



Invasive tumor	Choriocarcinoma	Placental site trophoblastic tumor
Invasive mole differs from hydatidiform mole only in its propensity to Direct myometrial invasion **with hydropic chorionic villi** and to metastasize.	Cytotrophoblasts and syncytiotrophoblasts **without chorionic villi**	
Edematous chorionic villi with trophoblastic proliferation that invade into the endometrium	Neoplastic syncytiotrophoblast and cytotrophoblast without chorionic villi	Absence of villi with proliferation of intermediate trophoblast cells (rare) (worst prognosis)

Signs and Symptoms:

Abnormal vaginal bleeding (the most common symptoms) **+ beta-hCG +ve**

Molar pregnancy

- Irregular or heavy vaginal bleeding during the 1st or early 2nd trimester of pregnancy.
- Absence fetal heart sound
- Expelion molar "grape like vesicles" from the vagina or may be detected in the vagina during pelvic examination.
- Lower abdominal pain
- **Endocrine Symptoms** (due to **high B-hCG** level):
  - **Hyperemesis gravidarum**,
  - **Hyperthyroidism**
- **Preeclampsia**
- In complete molar pregnancy, uterus size greater than normal for gestational age and usually associated with large ovarian (theca lutein) cysts

Malignant mole

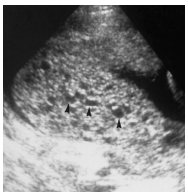
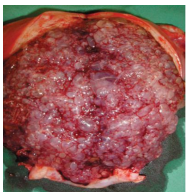
It may have subtle signs and symptoms of disease.

Vaginal bleeding more than 6 weeks following any pregnancy, normal or abnormal should be evaluated with testing to exclude a new pregnancy or GTD

Diagnosis :

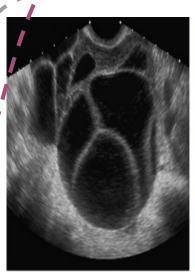
- **B-hCG (quantitative) :**
  - Elevated B-hCG level following normal or abnormal pregnancy and exclusion of pregnancy → GTN
  - if patient 10 wks pregnant & BHCG is 1000.000 → most likely molar.
    - The normal value at 10 wks is 100.000 which is the max or the plateau, then it starts slowly going down. This is the reason patients get hyperemesis gravidarum at 10 weeks → ↑ HCG
  - Increasing or plateau and B-hCG values after evacuation of a mole → post molar GTN

Definitive diagnosis of hydatidiform mole can usually be made ultrasonographically :

Complete Molar pregnancy:

- Diffuse, Heterogeneous hypoechogenicity pattern that is referred to as **snowstorm**
- No identifiable fetal parts.
- Theca lutein cysts




Theca lutein cysts is a normal finding in molar pregnancy → alpha HCG mimics LH → ovary stimulated

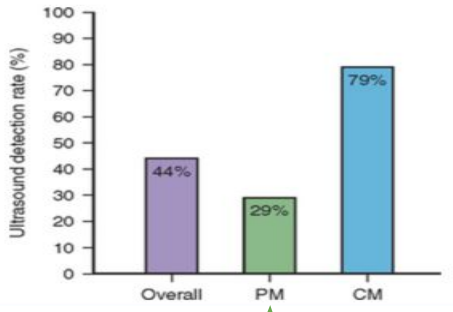
After evacuation and lowering of HCG the cysts spontaneously regress.


Partial molar pregnancy: when there's a baby or parts of a fetus with a hydropic placenta.

DDx: missed abortion, US can't tell the difference unlike in complete mole.

How good US is in diagnosing molar pregnancy?

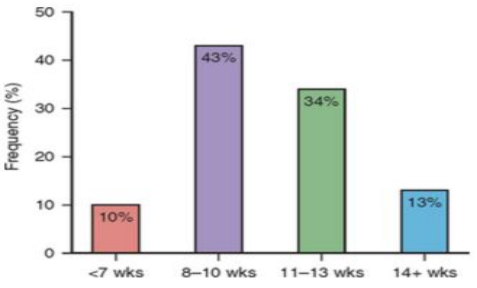
In complete molar 80% because of the **snowstorm appearance**



Due to DDx of missed abortion

At what gestational age diagnosis of molar pregnancy is made?

The majority of the cases are diagnosed before 13 weeks.



The earlier we diagnose the better the prognosis and treatment

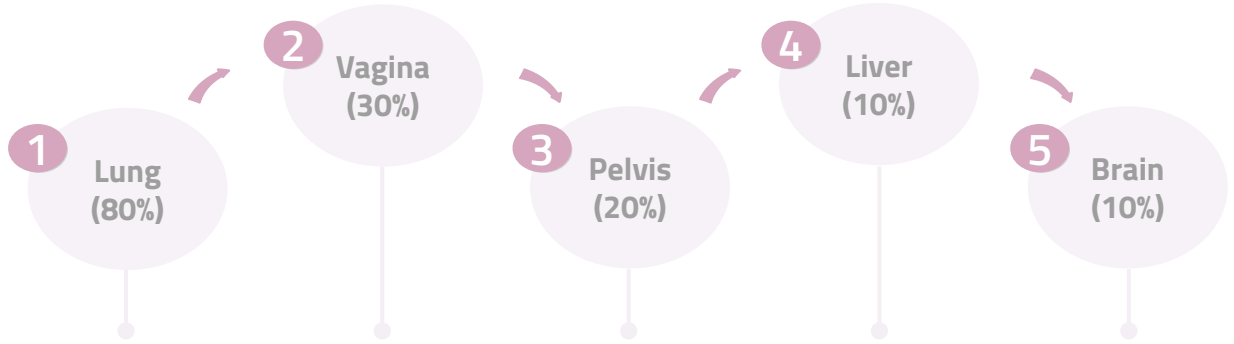
Even though we can suspect molar pregnancy from US findings, however the **definitive diagnosis is made through taking a biopsy (pathology) after doing D&C or by karyotyping**

Investigations :

- CBC (anemia, bleeding disorders, polycytosis, thrombocytopenia in DIC)
- Coagulation profile, bc patient may experience DIC (↑ INR, ↑ PT and PTT, ↓ fibrinogen)
- Liver and renal function tests
- Blood should be typed and cross-matched in the event that excessive bleeding is encountered at the time of evacuation of the mole. Also, important for the administration of anti-D, only in partial mole, in complete mole there are no fetal components.
- A Chest film

Metastasis

The most common sites of metastasis:



Treatment

- **MOLAR PREGNANCY :**
  - **Evacuation via suction dilation and curettage** and IV oxytocin is given simultaneously to help stimulate uterine contractions and reduce blood loss.
    - Risks of D&C: heavy bleeding and rarely it could cause Asherman syndrome
  - Hysterectomy (if patient desires surgical sterilization). Definitive management.

- **GTN without metastatic :**
  - Weakly chemotherapy : which will be IM methotrexate or IV actinomycin D with a cure rate close to 100%
  - **+/-** Hysterectomy : shorten the duration and amount of chemotherapy required, but it is not necessary for patients who wish to preserve childbearing.

- **GTN with metastatic :**
  - Treatment with multiagent chemotherapy, surgery +\- radiation.
    - Combination chemotherapy : Bagshawe regimen (6 drugs) : methotrexate actinomycin D, etoposide, vincristine, cyclophosphamide, and folinic acid.

- **Placental Site Trophoblastic Tumor :**
  - they are relatively insensitive to chemotherapy, so surgical resection of disease is important.

Prognostic scoring and management of GTN

- I just you to know that for patients with low risk GTN, we give them single agent chemotherapy and for patients with high risk GTN we give them EMA-CO.

Scores	0	1	2	4
Age	<40	>40	—	—
Antecedent pregnancy	Mole	Miscarriage	Term	—
Interval months from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum βhCG (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumour size (including uterus) (cm)	<3	3-4	≥5	—
Site of metastases	Lung	Spleen/kidney	Gastrointestinal	Liver/brain
Number of metastases	—	1–4	5–8	>8
Previous failed chemotherapy	—	—	Single drug	≥2 drugs

- **Case**: a patient with high persistent B-HCG of 200000, 4 months ago she received a single dose of methotrexate but cancer came back, she now presents with multiple lung metastasis, small brain nodule, treatment? EMA-CO

- Less than 7 (low score) or 7-12 (high score).
- Low score → single agent chemotherapy. (Methotrexate)
- High score → **5 agents (EMA-CO).**

Follow Up

All patients should have **weekly β-hCG** level measurements until **3 normal levels have been measured.**

- Patients with a **hydatidiform mole** should then have **monthly** level measurements until **6** normal levels have been measured.
- Patients with **GTN who have a good prognosis**, should have **monthly** levels until **12** normal measurements have been recorded.
- Patients with **GTN who have a poor prognosis** should have **monthly** levels until **24** normal measurements have been recorded.

If B-hCG levels plateau or rise at any time and chemotherapy should be initiated.

Contraception x6 months-OCP, depo provera or barrier methods **(**not IUD relatively contraindicated because uterine is fragile)
In cause of GTN patient has to be on contraception during treatment an for 1 year.

	Complete moles	Incomplete moles	Choriocarcinoma
PATH	• Completely molar = no fetal parts. • Completely chromosomal = 46 chromosomes. • Completely spermal = product of good fertilization and a bad egg (broken egg +single sperm a sperm doubles its chromosomes).	Incompletely molar = fetal parts are present Incompletely chromosomal = 69 chromosomes Incompletely spermal = product of good egg and a bad fertilization (good egg + 2 sperms)	malignant product of gestational content.
Pt	Size-date discrepancy, very elevated β-hCG, hyperthyroidism, hyperemesis gravidarum, vaginal bleeding (non-specific), grape like mass that protrudes from the cervix on vaginal exam, adnexal mass.		An elevated B-HCG after molar, aborted or normal pregnancy (worst prognosis).
Dx	**initial**: transvaginal U/S a snowstorm pattern.		**initial**: transvaginal U/S à snowstorm pattern. **Best**: biopsy obtained by a curettage **Then** stage with CT (lungs/brain).
Tx	Suction curettage (most **accurate** method of diagnosis and treatment and the same time).		**Surgical**: TAH for stage 1 (localized disease to the uterus) or debulking surgery for stage 3. **Medical**: Methotrexate+ Actinomycin D +/- Cyclophomide or aggressive chemo.
F/U	serial B-HCG while on OCP x12 months ;if there is a rise in B-HCG while on OCP = invasive gestational disease: invasive molar disease and choriocarcinoma.		

Teaching case

A 15-year-old primigravida presents for routine prenatal care. She is 14 weeks pregnant by last menstrual period. She has some nausea but otherwise feels well. The pregnancy to date has been unremarkable. She has support from her parents and the father of the baby. The uterus is enlarged, measuring 20 cm from the pubic symphysis. Fetal heart tones are not auscultated by Doppler. She denies vaginal bleeding or passage of tissue from the vagina. Vaginal exam is unremarkable. Routine prenatal labs were unremarkable. She is Rh-positive. Quantitative beta hCG levels were markedly elevated at 112,320 mIU/ml. TSH was low and further thyroid testing revealed the patient to be mildly hyperthyroid. Ultrasound showed the uterus to be enlarged, with multiple internal ehoes ad a so stor appearae. No fetus is oted. Ultrasound also showed enlarged multiloculated ovarian cysts bilaterally**.**

Q1 What is your diagnosis prior to receiving your ultrasound result?

- Poor dates, most likely if the patent's menses are irregular.
- Multiple gestation.
- Molar pregnancy (complete or partial) & malignant forms.
- Abortion (esp. missed)
- Ectopic pregnancy (not a top differential since B-HCG is high)
- Think of the anatomy (cervix, vagina, vulva…) any mass there or polyp or fibroid or trauma can cause bleeding, it could be a normal pregnancy but patient has threteaned abortion.

Q2 What aspects of the ultrasound guise the diagnosis?

- Ultrasound will evaluate the abnormal placental appearance of molar pregnancy and the presence (partial molar pregnancy) or absence of an associated fetus (complete molar pregnancy)
- Ultrasound will also reveal any associated ovarian enlargement.

Q3 What evaluation do you need to make a final diagnosis?

- Although ultrasound can diagnose gestational trophoblastic neoplasia; pathology is needed to confirm the diagnosis with or without malignant change.
- A chest x-ray is recommended prior to uterine evacuation to diagnose the likelihood of metastatic disease.
- In this context ultrasound is diagnostic of bilateral theca lutein cysts (no ovarian tissue is needed for this diagnosis).

Teaching case

Q4 What is the epidemiology and clinical course of this condition?

- Gestational trophoblastic neoplasia is the most curable gynecological malignancy. Although patients with hydatidiform mole are classically described as having a uterus that is large for dates, this only occurs in approximately half of the patients.
- Molar pregnancies are more likely to occur in women 15-years-old or less, or 40-years-old and greater.
- Ethnicity: Asian women are almost twice as likely to develop GTN as women of other ethnic groups.
- Gestational trophoblastic neoplasia is frequently associated with hyperthyroidism due to the release of a thyrotropin-like compound by the molar tissue.
- Patients with molar pregnancy have increased risk of trophoblastic disease in later pregnancies (recurrence rate is 1%) and should have early ultrasound in every subsequent pregnancy.

Q5 What is your management plan?

- Primary treatment is suction evacuation of the uterus.
- B-hCG should be followed regularly until negative, i.e. weekly until negative and then monthly for six months to a year.
- As patients with gestational trophoblastic neoplasia should not attempt subsequent pregnancy until after this time period, reliable contraception use needs to be discussed and implemented.
- If beta hCG does not rapidly decrease, consideration of post molar GTN must be considered (Methotrexate would be appropriate as secondary treatment).
- Thyroid function should also be followed until normalized.
- Chest x-ray and pelvic examination for uterine enlargement should be followed to rule out choriocarcinoma and to document the resolution of the ovarian cysts.

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Good Luck!

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