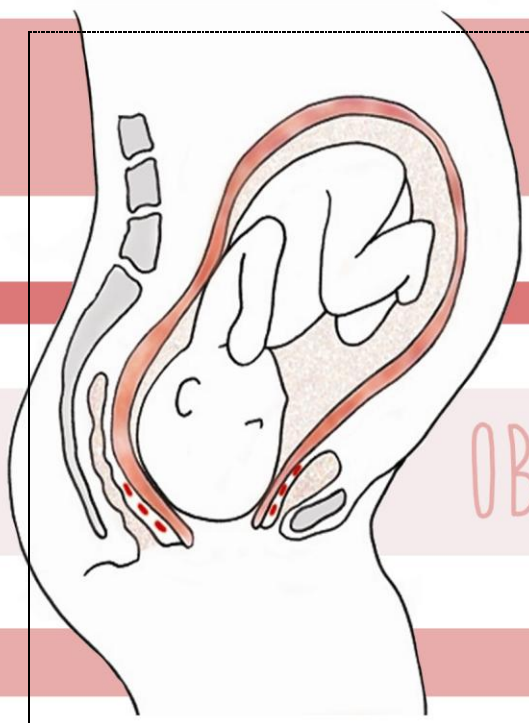

OBSTETRICS AND GYNECOLOGY

(Lecture 32) Gestational Trophoblastic Disease (GTD)

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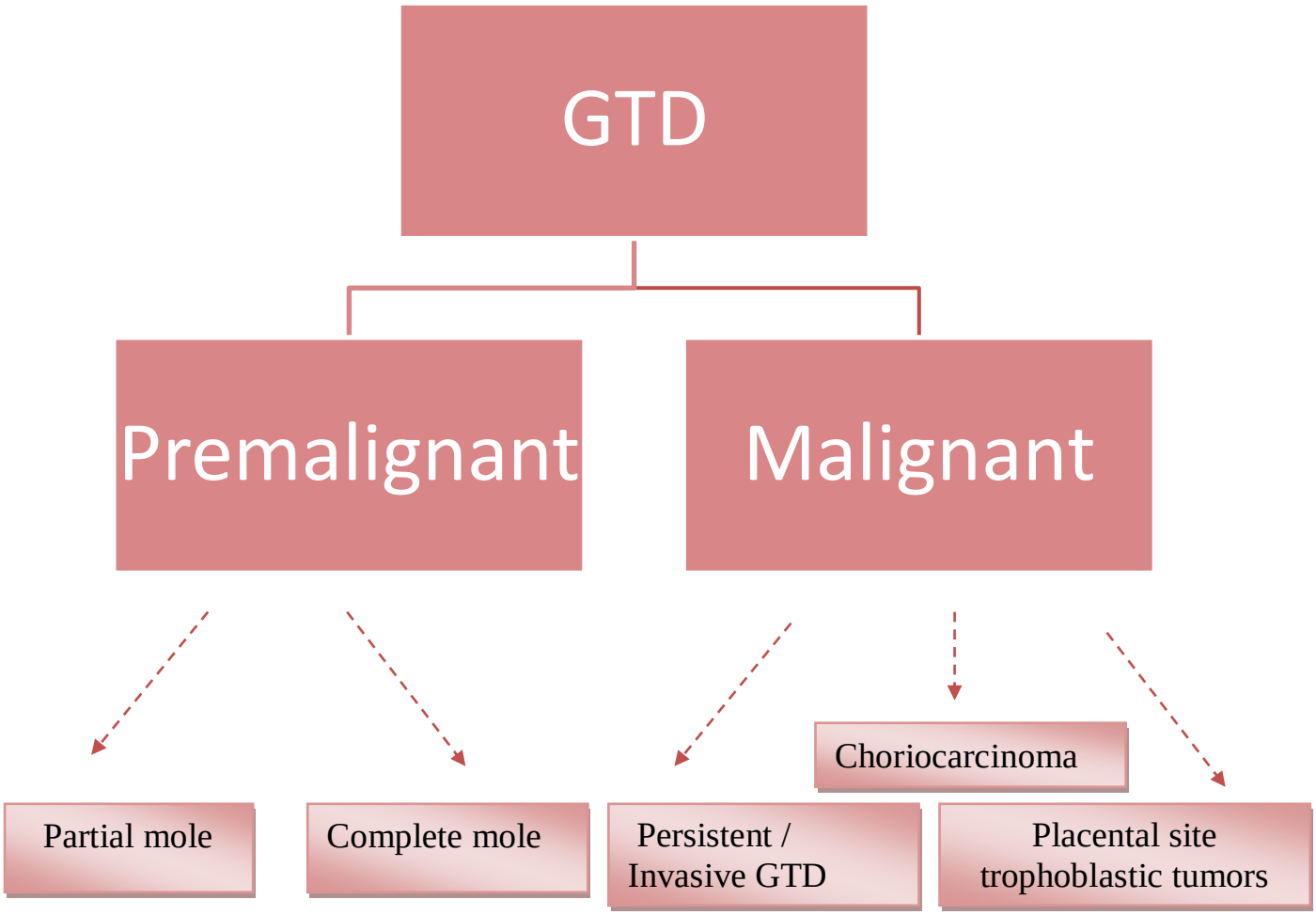
Objectives:

Not given



History and definition of GTD

Definition

GTN defines a heterogeneous group of lesions that represent an aberrant fertilization event the pathogenesis is unique because the maternal tumor arises from fetal tissue it is the most curable gynecologic malignancy.

Tumors in general are the person's own cells invade tissues and metastasize whereas in GTN it is the **embryo's cells** responsible for the invasion and metastases.

Classification and Epidemiology of GTD

- **Premalignant:**

1. Partial mole
2. Complete mole is more likely to become malignant than a partial mole, it is associated with increased risk of persistent disease and exaggerated symptoms.

- **Malignant:** grow very fast and has the ability to metastasize.

1. Persistent / Invasive GTD it started as premalignant type and then it progresses to this type.
2. Choriocarcinoma is the most **aggressive** type. It can start as a choriocarcinoma.
3. Placental site trophoblastic tumors.

Epidemiology

- Less than 1 in 1000 pregnancies in most of the world, 2 in 1000 in Japan (differences in diet) we can differentiate between genetic or environmental risk factors by looking at the cohort of immigrants that grow in another environment if they adapt the same risk of that environment it is environmental if they maintain their risk it is genetic.

Vitamin A deficiency in the rhesus monkey produces degeneration of the seminiferous epithelium with production of primitive spermatogonia and spermatocytes.

Risk Factors

- Women <15 years or >40 years of age getting pregnant
- Patients with previous history of molar pregnancy
- Possible other factors: deficiency of animal fat, Vitamin A and carotene, professional occupation, history of prior spontaneous abortion

Complete and partial moles

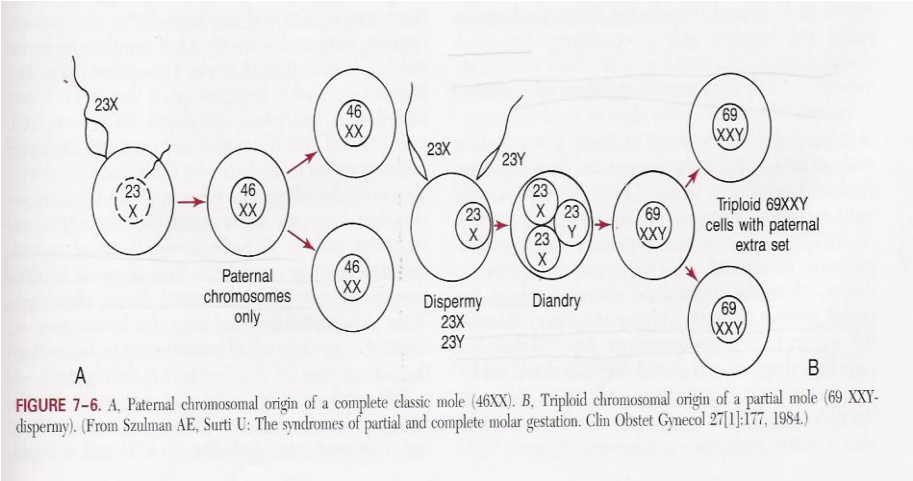


FIGURE 7–6. A, Paternal chromosomal origin of a complete classic mole (46XX). B, Triploid chromosomal origin of a partial mole (69 XXY-dispermy). (From Szulman AE, Surti U: The syndromes of partial and complete molar gestation. Clin Obstet Gynecol 27[1]:177, 1984.)

Beta-HCG level peaks at 10-12 (worst time because of the morning sickness, e.g. vomiting and nausea) then it starts to decline then it plateaus at 20 wks. Complete moles have very high levels of B-HCG with very bad symptom like: vaginal bleeding with abnormal vesicular tissue.

Complete moles:

23 chromosomes in one sperm fertilize an abnormal egg, which has no female genetic material. When one sperm enters an empty egg she may abort or may the sperm duplicates result in 46XX (normal number) but without maternal element. No fetal tissue. Everything is worse in this type and the chance of persistent GTD is higher.

Partial mole:

One sperm enters the egg, then another sperm enters due to any defect in Zona Pellucida which response to prevent that or maybe the same sperm duplicates result in 69XXY with maternal element. There will be fetal tissue like RBC or developed abnormal fetus. It is not bad as complete moles.

Symptoms and Signs

- Vaginal bleeding is the most common symptom. One of the differential diagnosis of bleeding in the first trimester is molar pregnancy.
- Patients with complete mole may have: first trimester pre-eclampsia, hyperthyroidism, hyperemesis, increased uterine size and theca-lutein cysts
- Patients with partial moles are diagnosed clinically as missed or incomplete abortion
- Nausea and vomiting because of high Beta-HCG level.

Diagnosis

In many patients the first evidence to suggest the presence of a hydatidiform mole is the passage of vesicular tissue

A quantative pregnancy test of greater than 100,000 IU/L, an enlarged uterus, and vaginal bleeding suggest a diagnosis of a hydatidiform mole
Ultrasound (test of choice) will show multiple echoes (snow storm).

β-hCG assays

The family of pituitary and placental glycoprotein hormones: HCG, FSH, LH and TSH, all have a common α-subunit and a distinct β-subunit
Many β-hCG assays are available, some detect intact β-hCG and others are selective for individual fragments
The competitive RIA using a polyclonal antibody recognizing all forms of **β-hCG remains a gold-standard** assay for use in the management of GTD
The amount of hCG produced corresponds with tumor volume so that a serum hCG of 5 IU/L corresponds to approximately 10,000 to 100,000 viable tumor cell.

Management

- **Evacuation curettage**: the method of evacuation
- RH –ve patients should receive Rhogam. We give it in both complete and partial because we aren't sure about the type, but the problem may happen in partial moles only because we have fetal tissue (like: RBC) in this type.
- IV oxytocin should be administered after a moderate amount of the tissue has been removed
- Complications may include: uterine perforation, hemorrhage, and trophoblastic embolization, infections.
- Hysterectomy may be selected as a method of evacuation in patients who desire sterilization.

Contraception

- We give OCP to be able to follow up the patient with Beta-HCG (should drop to zero if it drops and then plateaus that means she has persistent GTD), X-ray and CT scans.
- The risk of recurrence is highest in the first year after the evacuation. Usually they take it for 6 months after beta-HCG is zero.

➢ In a systemic review of the influence of OCPs in the development of post-molar trophoblastic neoplasia, two RCTs where included for analysis
➢ There was no clear evidence for an association between OCP use and the incidence of GTN was found

Gestational Trophoblastic Neoplasia (GTN)

- The hydatidiform mole precedes malignant disease in 50% of patients. There is an antecedent normal pregnancy in 25% of the patients and an abortion or ectopic pregnancy in the other 25%
- In many patients the preceding pregnancy occurred years before
- In other cases, patients with GTN may have no localized disease in the uterus and have only metastatic disease

Invasive Hydatidiform Mole

It is clinically identified by the combination of an abnormal uterine ultrasound scan and a persistent or rising B-HCG level **after** uterine evacuation of a molar pregnancy
Pathologic confirmation of invasion is rarely required.

Choriocarcinoma

- Highly malignant.
- Greater risk of hemorrhage and metastases.
- May arise from any type of pregnancy.

Nonmetastatic Trophoblastic Disease

- Disease is limited to the uterus
- Patients can be treated with single agent chemotherapy
- Treatment is 100% successful
- Single agent methotrexate or actinomycin D is the treatment of choice.

Good Prognosis Metastatic Trophoblastic Neoplasia

- Therapy can be the same as that described for nonmetastatic disease
- Methotrexate is considered by many to be the drug of choice.
- If resistant to methotrexate occurs, patients are switched to actinomycin D.

Who prognostic scoring system

➔ Patients who score between 0 and 6 receive low-risk chemotherapy.

➔ Patients scoring 7 or more are given high-risk treatment (combined chemotherapy EMACO).

Table 44–5. WHO Prognostic Scoring System as Modified by FIGO

Scores	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	
Interval (months) from index pregnancy	<4	4-<7	7-<13	≥13
Pretreatment serum human chorionic gonadotropin (IU/ L) level	$<10^3$	10^3-$<10^4$	10^4-$<10^5$	$\geq 10^5$
Largest tumor size (including uterus)	–	3-<5 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Brain, liver
Number of metastases identified	–	1-4	5-8	>8
Previous chemotherapy failed	–	–	Single drug	Two or more drugs

Work Up of Gestational Trophoblastic Neoplasia

Chemotherapy

GTN is Sensitive to chemotherapy

a. Single-agent chemotherapy (for treating nonmetastatic disease)

i. Methotrexate or actinomycin D

ii. Cure rate up to 100%

b. Combined chemotherapy for treatment of metastatic disease International Federation of

Gynecology and Obstetrics (FIGO) score ≥ 7

i. EMACO [Etoposide, Methotrexate, Actinomycin D, Cyclophosphate, Oncovin]

ii. Cure rate up to 80%–90%

c. Adjunctive radiotherapy is used for patients with brain metastasis.

Table II-6-3. Gestational Trophoblastic Neoplasia—Basic Approach

β-hCG titer	Baseline for future comparison
Chest x-ray	Lung metastasis is ruled out
Suction D&C	Empty uterus contents
Oral contraceptive pills for 1 year	Prevent confusion: recurrent disease and normal pregnancy

Table 7–5. WORK-UP OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

History and physical examination
Chest film
Pretreatment hCG titer
Hematologic survey
Serum chemistries
Computed tomography scan of the brain } only if above
Ultrasound of the pelvis } denotes abnormality
Liver scan

hCG, human chorionic gonadotropin.

Drug-resistant disease

- CT of the chest and abdomen together with MRI of the brain and pelvis is often helpful and can detect deposits not previously seen.

The role of repeat uterine evacuation in the management of persistent GTD

- After a second uterine evacuation 68% of the patients (368 patients) had no further evidence of persistent disease and did not require chemotherapy.
- Chemotherapy was more likely when the hCG level is ›1500 IU/L.
- Third evacuation is not recommended.

Poor Prognosis Metastatic Trophoblastic Neoplasia

- Multiple agent chemotherapy is recommended in this disease.
- EMA-CO is considered the regimen of choice in most high-risk patients (Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, Vincristin).
- The overall survival rate for these patients is 80-85%.
- Patients with cerebral or hepatic metastases are treated concurrently with **radiotherapy** for the whole brain or liver (for hemostasis).
- Surgery is not necessary in most patients; it may play a role in cases of tumor resistance to chemotherapy.

Site of metastasis: lung, vagina, CNS, kidney, liver.

Persistent Low HCG Levels

- Pituitary HCG
- False +ve HCG results
- Quiescence GTD

Placental Site Trophoblastic Tumor

- Rare tumors (account for 0.23% cases of GTD).
- It has a variety of clinical features and its course is unpredictable.
- Can appear shortly after termination of pregnancy or years later.
- **Hysterectomy** is considered optimal therapy and is usually adequate in most situations.
- Chemotherapy can still play a major role.

Future Childbearing

- After treatment of GTN, molar pregnancies occur in only about 1-2% of subsequent pregnancies.
- These patients should be evaluated with a **first trimester ultrasonography.**
- Pregnancy outcome in women with history of molar gestation is similar to those with no such history.
- Standard chemotherapy protocols have minimal impact on the subsequent ability to reproduce.

Doctor's notes:

- Dilatation and Curettage "D&C" are used for diagnosis, if hCG levels start to increase after the procedure start investigating with basic blood tests, US and CXR, if the were negative then the patient is low risk, if one is positive start looking for metastasis.

- If there is signs of metastasis, start with Methotrexate for low risk patients and EMACO therapy for high risk patients.

- The longest the period between the evacuation and hCG rise the worst the condition.

- High beta-hCG with mass, with/without tissue in the uterus, start chemotherapy with histopathological evidence because the patient might bleed from touching the tumor.

- Methotrexate won't affect the patient's fertility.

MCQs:

Q1. A 22-year-old, G1PO, presents to the emergency room with 5 days of worsening nausea and vaginal bleeding. Last menstrual period (LMP) was 10 weeks ago. Pelvic examination is significant for a 14-week- sized uterus. Quantitative human chorionic gonadotropin (hCG) level is 120,000 units/mL, and ultrasound imaging reveals material within the endometrial canal that has a "snowstorm" appearance. There are no fetal parts seen. The patient undergoes an uncomplicated dilation and evacuation in the operating room, and the tissue is sent for genetic testing. What is the most likely genetic constitution of the specimen?

a. 69, XXX
b. 69, XXY
c. 46, XX
d. 46, XY

Q2. A 28-year-old, G3P2, presents to clinic for routine obstetric care. Last menstrual period (LMP) was 12 weeks ago. A 10-week-sized uterus is found on pelvic examination, and a subsequent ultrasound reveals a grossly abnormal fetus without cardiac activity. The patient opts for uterine evacuation. Pathology inspection notes the presence of fetal parts, focal villous edema, and focal trophoblastic proliferation. What is the most likely genetic constitution of the specimen?

a. 46, XX
b. 46, XY
c. Triploidy
d. Aneuploidy

Q3. An otherwise healthy 24-year-old GO presents to her gynecologist because of irregular, heavy vaginal bleeding for the past few days. She also complains of worsening nausea, vomiting, headache, and dizziness over the past few weeks. She reports that her last regular menstrual period before her current bleeding started was 6 weeks ago. On examination, she has a slight tremor in both hands, an enlarged 10-week- sized uterus, and blood coming from the cervical os. Urine (3-hCG is positive. Vital signs are temperature 36.8, heart rate 100 beats/min, blood pressure 160/100 mmHg, and respiratory rate 16 breaths/min. What is the most likely diagnosis?

a. Missed abortion
b. Incomplete abortion
c. Gestational hypertension
d. Molar pregnancy
e. Ectopic pregnancy

Q4. A 28-year-old, G1PO, presents to the emergency department with hemoptysis. She reports that she has had increasing cough and shortness of breath over the past 8 weeks and that she coughed up a dime-sized blood clot this morning. On review of systems, the patient endorses heavy and irregular vaginal bleeding. She says that she had a spontaneous abortion 6 months ago and that she started having increasingly irregular and heavy periods about 4 months ago. On examination, her uterus is enlarged to 12-week size. Serum [3-hCG is elevated, hemoglobin is 10 mg/dL, and chest X-ray reveals two dense areas in her lungs, one in the right upper lobe and one in the left lower lobe. Which of the following is the most likely diagnosis?

a. Missed abortion
b. Incomplete abortion
c. Choriocarcinoma
d. Molar pregnancy
e. Ectopic pregnancy

Q5. A 35-year-old G2Pl presents with scant first-trimester bleeding. An ultrasound report describes an empty gestational sac. Which of the following statements is correct regarding this presentation?

a. It is caused by an abnormality of the placenta
b. It is the result of a genetic error
c. The quantitative f3-hCG is likely to be unusually low
d. It is most often due to paternal causes
e. The risk of severe hemorrhage is increased

Answers

Q1: C

Q2: C

Q3: D

Q4: C

Q5: B

Explanation:

Q1: Complete moles have chromosomes entirely of paternal origin as a result of fertilization of a blighted ovum by a haploid sperm that replicates. Rarely fertilization of a blighted ovum by two sperm occurs. The karyotype of a complete mole is usually 46, XX and rarely 46, XY. Partial hydatidiform moles result from double fertilization of a normal haploid egg or from fertilization by a diploid sperm. The karyotype is 69, XXX or 69, XXY. Complete moles are more common than partial moles and are more likely to undergo malignant transformation.

Q2: In cases of partial mole, the ultrasound reveals an abnormally formed fetus. The fetus of a partial mole is usually a triploid and results from dispermic fertilization of a normal ovum. This consists of one haploid set of maternal chromosomes and two haploid sets of paternal chromosomes. Pathology inspection of partial moles typically shows focal villous edema and focal trophoblastic proliferation. Diffuse villous edema and trophoblastic proliferation are usually found with complete moles.

Q3: This patient has numerous findings that are consistent with a molar pregnancy. The most common presenting symptom for a molar pregnancy is heavy or irregular bleeding early in pregnancy, and physical examination reveals size greater than dates in about half of the patients. A molar pregnancy also produces high levels of hCG, which can lead to nausea and vomiting. The a-subunit of hCG is structurally identical to that found in thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Therefore, patients with molar pregnancies may also have signs of hyperthyroidism, like nervousness, anorexia, or tremor, as well as large theca lutein cysts on the ovaries from stimulation by an LH/FSH analog. In a patient without baseline hypertension (such as this patient), preeclampsia before 20 week's gestation is highly suggestive of a molar pregnancy. A missed abortion, an incomplete abortion, pure gestational hypertension, or an ectopic pregnancy would not have this constellation of symptoms.

Q4: This woman's presentation is concerning for choriocarcinoma metastatic to the lungs. Choriocarcinoma is a malignant tumor that can arise in the uterus after any pregnancy. Approximately half of the choriocarcinomas occur after molar pregnancies, one-quarter after normal term pregnancies and one-quarter after abortion (spontaneous or therapeutic) and ectopic pregnancies. The most common presentation is heavy and irregular vaginal bleeding, and many patients present with the signs of metastatic disease. The most common metastatic locations include the lung and the central nervous system, but choriocarcinoma is notorious for metastasizing anywhere.

Q5: The quantitative f3-hCG is likely to be unusually low. The remainder of the responses refer to molar pregnancy, which typically presents with sonographic findings of a snowstorm pattern. In cases of molar pregnancy, the f3-hCG is typically very elevated above what would be expected for the same gestation of a normal pregnancy, there is an increased risk of hemorrhage, and the culprits for this placental condition are paternal X chromosomes.

For mistakes or feedback

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