Obstetrics & Gynecology
TEAM

Gestational Trophblastic Neoplasia (GTN)

Leader: Sara Alhaddab

Done By: Jumana AlShammari

◆very important ◆mentioned by doctor ◆team notes ◆not important

Gestational Trophblastic Neoplasia (GTN):

History of GTN:

- The first record of gestational trophoblastic disease (GTD) probably dates to 400 BC, when Hippocrates described "dropsy of the uterus"
- In 1276, the attendants of Margaret Countess of Henneberg noticed that her abnormal delivery consisted of multiple hydropic vesicles

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

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

Introduction:

Clinical spectrum that includes all neoplasms that derives from abnormal placental (trophoblastic) proliferation.

A. Benign disease: hydatidiform molar pregnancy (most common)

B. Malignant disease:

1. Invasive trophoblastic disease, choriocarcinoma, placental site trophoblastic tumors
2. 20% of patients with benign molar disease develop malignant disease

Classification:

- Benign:
  1. Partial mole:
  2. Complete mole:
- Malignant:
  1. Persistent / Invasive GTD
  2. Choriocarcinoma
  3. Placental site trophoblastic tumors

A complete mole is more likely to become malignant than a partial mole

Epidemiology:

- Less than 1 in 1000 pregnancies in most of the world, 2 in 1000 in Japan (differences in diet)
- Vitamin A deficiency in the rhesus monkey produces degeneration of the seminiferous epithelium with production of primitive spermatogonia and spermatocytes

Studied incidence in immigrants (Japanese) living in the USA and discovered that these immigrants have the same risk as the population they live in that means it is related to environment not genetics

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:

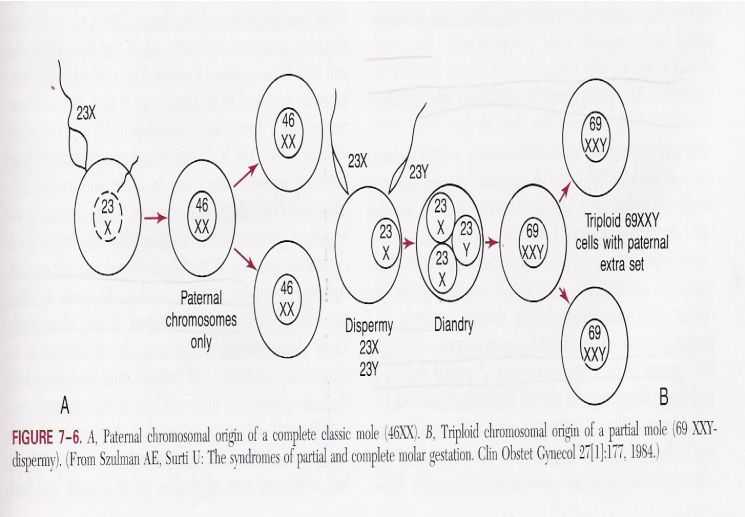


FIGURE 7-6. A, Paternal chromosomal origin of a complete classic mole (46XX). B, Triploid chromosomal origin of a partial mole (69 XXY-dispermy). (From Szulman AE, Surti U: The syndromes of partial and complete molar gestation. Clin Obstet Gynecol 27[1]:177, 1984.)

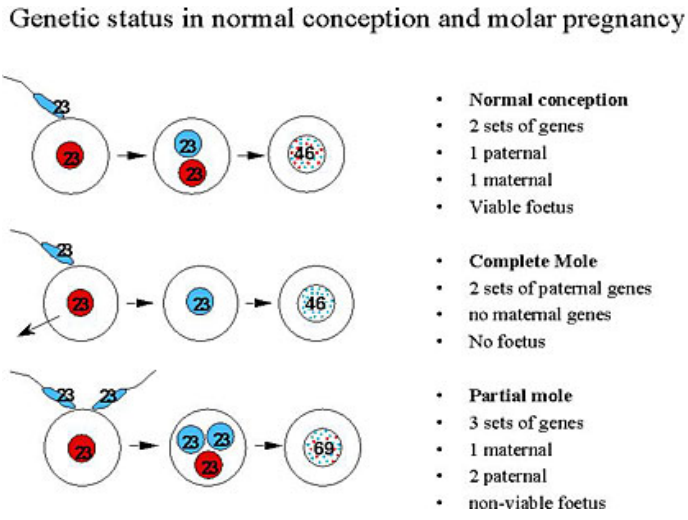


Table II-6-1. Benign Gestational Trophoblastic Neoplasia—H Mole

Complete	Incomplete
Empty egg	Normal egg
Paternal X's only	Maternal and paternal X's
46,XX (**di**ploidy)	69,XXY (**tri**ploidy)
Fetus absent	Fetus nonviable
20% → malignancy	10% → malignancy
No chemotherapy; serial β-hCG titers until (–); follow-up 1 year on oral contraceptive pill	

Even though in the complete mole the number of chromosomes might seem normal but they are all paternal unlike the incomplete (partial) mole

Symptoms and signs:

- Vaginal bleeding prior to 16 weeks' gestation is the **most common** symptom and passage of vesicles from the vagina.
- Patients with complete mole may have: first trimester pre-eclampsia, hyperthyroidism, hyperemesis, increased uterine size and theca-lutein cysts
- The **most common** sign is fundus larger than dates, absence of fetal heart tones, bilateral cystic enlargements of the ovary known as **theca-lutein cysts**.
- Patients with partial moles are diagnosed clinically as missed or incomplete abortion
- Excessive nausea/ emesis (because of high β-hCG levels)

One of the differential diagnosis to bleeding in the first trimester is molar pregnancy

TABLE 46.1 Features of Partial and Complete Hydatidiform Moles

Feature	Partial Mole	Complete Mole
Karyotype	Triploid	46,XX, rarely 46,XY
Pathology		
Fetus	Often present	Absent
Amnion, fetal RBCs	Usually present	Absent
Villous edema	Variable, focal	Diffuse
Trophoblastic proliferation	Focal, slight to moderate	Diffuse
Clinical presentation		
Diagnosis	Missed abortion	Molar gestation
Uterine size	Small or appropriate for gestational age	50% large for gestational age
Theca lutein cysts	Rare	>25% depending on diagnostic modality
Medical complications	Rare	Becoming rare with early diagnosis
Postmolar invasion and malignancy	<5%	15% and 4% respectively

RBCs, red blood cells.
(Table modified from *ACOG Practice Bulletin #53* June 2004. Updated information from Berkowitz RS, Goldstein DP. Gestational trophoblastic disease. In: Hoskins WJ, Perez CA, Young RC, eds. *Principles and Practice of Gynecologic Oncology*, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:1057–1061.)

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 cells.

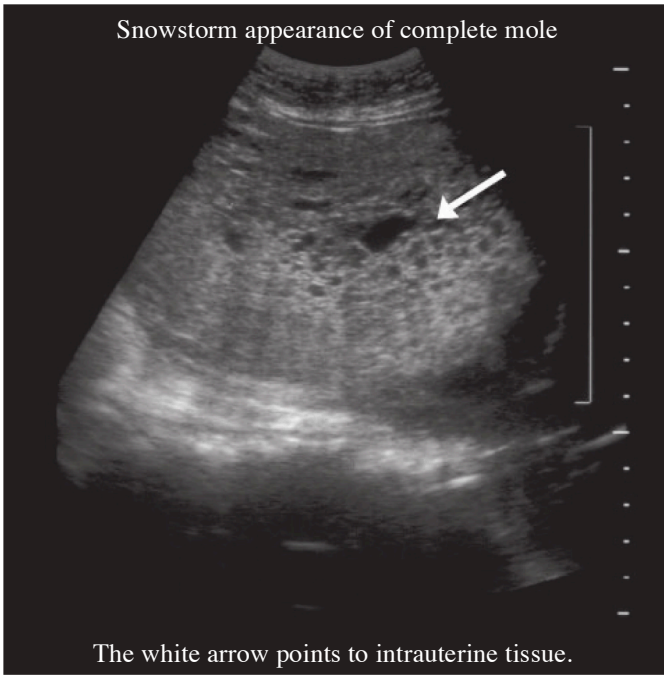
Diagnosis:

- In many patients the first evidence to suggest the presence of a hydatidiform mole is the passage of vesicular tissue
- A quantative pregnancy test (hCG levels) of greater than 100,000 IU/L, an enlarged uterus, and vaginal bleeding suggest a diagnosis of a hydatidiform mole
- Ultrasound is the **test of choice** will show multiple echoes (snowstorm)

Management:

- Evacuation curettage: the method of evacuation
- RH –ve patients should receive Rhogam
- IV oxytocin should be administered after a moderate amount of the tissue has been removed
- Complications may include: uterine perforation, hemorrhage, and trophblastic embolization
- Hysterectomy may be selected as a method of evacuation in patients who desire sterilization
- Baseline quantitative β-hCG titer
- Chest X-ray to rule out lung metastasis

Place the patient on effective contraception (oral contraceptive pills) for the duration of the follow-up period to ensure no confusion between rising b-hCG titers from recurrent disease and normal pregnancy.



Snowstorm appearance of complete mole

The white arrow points to intrauterine tissue.

Contraception:

- In a systemic review of the influence of Oral Contraceptive Pills (OCP) in the development of post-molar trophblastic neoplasia, two randomized controlled trials (RCT) where included for analysis.
- There was no clear evidence for an association between OCP use and the incidence of GTN was found.

Table 7–1. MANAGEMENT OF HYDATIDIFORM MOLE

1. β-hCG determination every 1–2 weeks until negative twice
   a. Then bimonthly for 1 year
   b. Contraception for 6–12 months
2. Physical examination, including pelvic every 2 weeks until remission
   a. Then every 3 months for 1 year
3. Chest film initially
   a. Repeat only if hCG titer plateaus or rises
4. Chemotherapy started immediately if:
   a. hCG titer rises or plateaus during follow-up
   b. Metastases are detected at any time

hCG, human chorionic gonadotropin.

Gestational Trophblastic 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.

The **most common site of distant metastasis** is the **lungs**.

Invasive Hydatidiform Mole:

- It is clinically identified by the combination of an abnormal uterine ultrasound scan and a persistent or rising β-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

Table 7–2. CLASSIFICATION OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

Nonmetastatic disease: no evidence of disease outside the uterus
Metastatic disease: any disease outside the uterus
Good prognosis metastatic disease
1. Short duration (last pregnancy <4 months)
2. Low pretreatment hCG titer (<100,000 IU/24 hr or <40,000 mIU/ml)
3. No metastasis to brain or liver
4. No significant prior chemotherapy

Poor prognosis metastatic disease
1. Long duration (last pregnancy >4 months)
2. High pretreatment hCG titer (>100,000 IU/24 hr or >40,000 mIU/ml)
3. Brain or liver metastasis
4. Significant prior chemotherapy
5. Term pregnancy

hCG, human chorionic gonadotropin.

Nonmetastatic Trophblastic 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

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 Trophblastic Neoplasia:

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
Ultrasound of the pelvis
Liver scan
} only if above denotes abnormality

hCG, human chorionic gonadotropin.

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 [**E**toposide, **M**ethotrexate, **A**ctinomycin D, **C**yclophosphate, **O**ncovin]
   ii. Cure rate up to 80%-90%

c. Adjunctive radiotherapy is used for patients with brain metastasis

Table 7–6. SINGLE-AGENT CHEMOTHERAPY

1. Methotrexate 20–25 mg IM every day for 5 days (repeat every 7 days if possible)
2. Dactinomycin 10–12 μg/kg IV every day for 5 days (repeat every 7 days if possible)
3. Methotrexate 1 mg/kg IM on days 1, 3, 5, and 7; folinic acid 0.1 mg/kg IM on days 2, 4, 6, and 8 (repeat every 7 days if possible)
4. Methotrexate 30 mg/m² weekly

IM, intramuscular; IV, intravenous.

Table 7–7. MANAGEMENT OF SINGLE-AGENT CHEMOTHERAPY

A. Chemotherapy
   1. Repeated at 7–10 days intervals depending on toxicity
   2. Contraception begun (oral if not contraindicated)
B. Drug continued as above until the hCG titer is normal
C. Chemotherapy changed if:
   1. Titer rises (10% or more)
   2. Titer plateaus
   3. Evidence of new metastasis
D. Laboratory values—chemotherapy not repeated unless:
   1. WBC >3000/mm³
   2. Polys >1500/mm³
   3. Platelets >100,000/mm³
   4. BUN, SGOT, SGPT essentially normal
E. Other toxicity mandating postponement of chemotherapy
   1. Severe oral or gastrointestinal ulceration
   2. Febrile course (usually present only with leukopenia)
F. Remission defined as three consecutive normal weekly hCG titers

BUN, blood urea nitrogen; hCG, human chorionic gonadotropin; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamate pyruvate transaminase.

Table 7–8. REMISSION AND FOLLOW-UP IN GESTATIONAL TROPHOBLASTIC NEOPLASIA

1. Three consecutive normal weekly hCG assays (1–3 courses after normal)
2. hCG titers every 2 weeks for 3 months
   Then monthly for 3 months
   Then every 2 months for 6 months
   Then every 6 months
3. Frequent pelvic examination
4. Contraception for at least 6 months

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.

Sites of metastasis: **lungs**, vagina, CNS, kidney, liver.

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

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

From Step Up

- Secretes small amounts of hCG
- Rarely metastatic
- Resistant to standard chemotherapy

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