Gestational trophoblastic disease (GTD)

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Abstract

Gestational trophoblastic disease comprises hydatidiform mole (complete and partial) and gestational trophoblastic neoplasia. The epidemiology, clinical features, and diagnosis of each of these trophoblastic disease types are discussed. Importance is given to management of hydatidiform mole prophylactic chemotherapy. Around 10% of all hydatidiform moles become malignant; an estimated 8-15% of complete and 1.5-6% of partial hydatidiform moles.

Key words: Gestational trophoblastic disease, Gestational trophoblastic neoplasia & hydatidiform mole

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Introduction

Gestational Trophoblastic Disease (GTD) represents a spectrum of diseases which arise from abnormal trophoblastic tissue. This ranges from the benign hydatidiform mole ("molar pregnancy") through to the malignant invasive mole, choriocarcinoma and placental site tumors (PSTT). Though these diseases are relatively rare, GTD is a completely curable disease; nevertheless, correct diagnosis and vigilant follow-up is important in order to maximize the outcome for these patients.

Epidemiology

It is hard to describe the occurrence and etiologic factors which can results in the development of GTD. There are many factors that hinder in accumulating reliable epidemiologic data, such as irregularities in case definitions, failure to adequately describe the population at risk, no centralized records, and rarity of the diseases.

An estimated 1-3/1000 pregnancies are affected by benign hydatidiform moles. The prevalence varies from one country to another: the rates are double in Southeast Asia among Eurasians people as compared with Chinese, Malaysian, or Indian origin. It is estimated in United State the rate is to be around 0.75-1/1000.

Around 10% of all hydatidiform moles become malignant; an estimated 8-15% of complete and 1.5-6% of partial hydatidiform moles. Around 8% of women with a previous molar pregnancy will develop persistent trophoblastic disease (i.e. recurring hydatidiform moles). In India, post-molar GTD was recorded 20.4%, which is very high, but still accurate figures are ambiguous.

Risk factors for GTD

- **Age:** Women ages 16-39 are high risk to develop a molar pregnancy. The risk to develop GTD increases three times in women aged over 50 who become pregnant.
- **Asian ethnicity**: It is estimated of higher incidence of GTD in the Asian region. Women of Asian ethnicity are almost twice as likely to develop GTD as women of non-Asian ethnicity.
- **Previous molar pregnancy**: About half of all choriocarcinoma seems in women who have previous history of GTD and almost one in seven pregnancies occurring in this group is most likely to be molar pregnancy.
- **Family history of molar pregnancy**: GTD has genetic causes which results from genetic mutation of a 19 chromosome.
- **Dietary Factors**: Low intake of carotene and animal fat has been associated with increased risk of complete hydatidiform, as has Vitamin A deficiency.

Table 1: Types and Clinical features of gestational trophoblastic disease

Types	Clinical features
Hydatidiform mole, complete	15-20% trophoblastic sequelae hCG often _100,000 mIU/mL Medical complications
Hydatidiform mole, partial	_5% trophoblastic sequelae hCG usually _100,000 mIU/mL Rare medical complications
Invasive mole	15% metastatic–lung/vagina Most often diagnosed clinically
Choriocarcinoma	Vascular spread to distant sites–lung/brain/liver Malignant disease
PSTT (placental site trophoblastic tumor)	Extremely rare hCG levels less reliable indicator Relatively chemoresistant Mainly surgical treatment
hCG: human chorionic gonadotropin.	

General Symptoms: The most common symptom are:

- Vaginal bleeding
- Abdominal pain
- Excessive nausea and vomiting (more than normal during early pregnancy).
- However many women with a molar pregnancy may not show any symptoms.
- Anemia in case severe bleeding

If metastasis occurs, symptoms include:

- **Lung metastasis**: Coughing up of blood or experiencing shortness of breath, chest pain
- **Brain metastasis**: Dizziness, fainting, seizures or headaches.
- **Vaginal**: Vaginal bleeding or pus like discharge.
- **Liver**: Abdominal pain, yellowing of skin and eyes.

Diagnosis

1. **Urine and blood levels of hCG**: Taking measurements of the hormone, human Chorionic Gonadotropin (hCG) (levels of which are elevated during pregnancy) may give good indication, in most of the cases the levels are very high.
2. **Ultrasound**: Ultrasound in the first trimester may not be reliable. The typical 'snowstorm' appearance occurs mainly in the second trimester, showing a heterogeneous mass with no fetal development, and theca-lutein ovarian cysts.
   - Because of the lack of diagnostic reliability of ultrasound, products of conception from all non-viable pregnancies should undergo histological examination in order not to miss the diagnosis, and the chance of monitoring to prevent complications.
   - When there is diagnostic doubt about the possibility of a combined molar pregnancy with a viable fetus then ultrasound examination should be repeated before intervention.
3. **Imaging tests:** Imaging tests like x-rays, magnetic fields, or radioactive substances to create pictures of the inside of body may be done to help find out whether a tumor is present and to learn how far it may have spread.

Staging investigations where metastatic disease is suspected:

- Doppler pelvic ultrasound for local pelvic spread and vascularity.
- CXR or lung CT scan to diagnose lung metastases.
- CT scanning for liver or other intra-abdominal metastases.
- MRI scanning for brain metastases.

Progression

- **Spontaneous resolution**: Spontaneous resolution may occur by the mole is expelled from the body via the vagina, in circumstances very similar to a miscarriage and no treatment is necessary.
- **Develop to invasive hydatidiform moles**: Hydatidiform moles may transform to malignant moles and metastasize. An estimated 8-15% of complete and 1.5-6% of partial moles take this course.
- **Develop to persistent trophoblastic disease**: About 8% of patients experience recurring hydatidiform moles, they may be requiring chemotherapy following surgical treatment.

Management

Surgical treatment: There are two types of surgical techniques which can be used to treat non-metastatic GTD, dilatation and curettage and hysterectomy.

Chemotherapy

Indications for chemotherapy in GTD:

- Plateaued or rising hCG levels after evacuation.
- Histological evidence of choriocarcinoma.
- Evidence of metastases in the brain, liver, or gastrointestinal (GI) tract, or radiological opacities >2 cm on CXR.
- Pulmonary or vaginal metastases.
- Heavy vaginal bleeding or evidence of GI or intra-peritoneal hemorrhage.
- Serum hCG greater than 20,000 IU/L more than four weeks after evacuation, because of the risk of uterine perforation with further evacuation attempts.

Chemotherapy regimes

Women with evidence of persistent GTD should undergo assessment of their disease followed by chemotherapy. Disease risk is scored according to the FIGO staging for GTD.

Table 2: World health organization prognostic index score for gestational trophoblastic disease

Risk factor	0	1	2	4
Age	≤ 39	>39		
Antecedent pregnancy	Hydatidiform Mole	Abortion	Term	
Interval (months) from antecedent pregnancy	<4	4 to 6	7 to12	>12
Human chorionic gonadotrophin (HCG) (IU/L)[b]	$<10^3$	-10^4	-10^5	$>10^5$
ABO blood group (female × male)		O × A A × O	AB	B
Largest tumor mass, including uterine(cm)		3 – 5	>5	
Site of Metastases		Spleen	GI tract	Brain
Number of metastases		1 - 4	5 - 8	>8
Prior chemotherapy			Single drug	Two or more

[a]Interval = time (months) between end of antecedent pregnancy and start of chemotherapy
[b] Immediate pre-therapy plasma HCG level
Risk groups:
≤4 low-risk group
5 to 7 middle – risk group
≥8 high – risk group

AIlancheran. Optimal Treatment in Gestational Trophoblastic Disease. Annals Academy of Medicine. September 1998: 27(5);698-704

The total score is obtained by adding the individual prognostic factors. Scores from 0-6 are categorized as low risk, while a score of 7 or higher is high risk.

Chemotherapy regimen for low-risk patients with Gestational Trophoblastic Disease

Methotrexate 50 mg intramuscularly; repeated every 48 hours (total of four doses) - courses are repeated every two weeks.

- Calcium folinate (folinic acid) 15 mg orally 30 hours after each injection of methotrexate.

Chemotherapy regimen for high-risk patients with GTD

There is no strong evidence to determine the best combination chemotherapy regimen for high-risk gestational trophoblastic tumor. Therefore, the most clinically practiced drug therapy is:

Day 1: etoposide, methotrexate and dactinomycin. Day 2: etoposide, dactinomycin and folinic acid rescue (starting 24 hours after beginning the methotrexate infusion).	Day 8: cyclophosphamide and vincristine (on day 8 only).

This schedule is known as EMA/CO (= etoposide/ methotrexate/ dactinomycin - formerly actinomycin D/ cyclophosphamide/ vincristine - formerly oncovin). Treatment is continued until hCG levels have returned to normal, and then for a further six consecutive weeks.

Follow-up after chemotherapy

- Women are followed up for life following chemotherapy because there is no certainty about when it is safe to stop monitoring.
- Initially urine and serum hCG levels are monitored weekly; this gradually drops to four-weekly urine levels in year 2, and through further gradual reductions in frequency to six-monthly levels from year 6.
- The highest risk of recurrence is in the first year.

Future pregnancy

- Women being monitored after molar pregnancy should be advised not to conceive until their hCG levels have been normal for six months. Women who undergo chemotherapy are advised not to conceive for one year after completion of treatment.

Contraception and hormone replacement therapy

- Women with GTD should be advised to use barrier methods of contraception until hCG levels revert to normal. Once hCG levels have normalized, the combined oral contraceptive pill (COCP) may be used.

- If oral contraception has been started before the diagnosis of GTD was made, the woman can be advised to remain on oral contraception but she should be advised that there is a potential complications but low increased risk of developing GTN.
- The small potential risk of using emergency hormonal contraception, in women with raised hCG levels, is outweighed by the potential risk of pregnancy to the woman.

Complications of Hydatidiform Mole

Common complications include anemia, hyperthyroidism, pregnancy-induced hypertension or pre-eclampsia, and theca lutein cysts.

Anemia: Hemoglobin of less than 10 g/dL, seen in 50% of patients with complete moles and results from excessive vaginal bleeding

Pre-eclampsia: Occurs in approximately 25% of cases and presents with the signs and symptoms of pre-eclampsia seen in non-molar pregnancies [hypertension (HTN), proteinuria, edema].

Hyperthyroidism: Seven percent of patients with complete moles present with hyperthyroidism, with clinical findings of tachycardia, HTN, and tachypnea.

These patients should receive beta-sympathetic blockade before induction of anesthesia to prevent thyroid storm, which can be precipitated by surgery itself.

Theca lutein cysts(cysts >6 cm) are observed in 50% of patients and result from hCG stimulation. These cysts may require 2 to 4 months to resolve completely. Persistent cysts warrant appropriate workup and possible surgical management.

Pulmonary distress is observed in 2% of patients. Frequently, it occurs at the time of evacuation of a mole in patients with marked uterine enlargement.

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