

# Gestational Trophoblastic Disease

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## Summary

Gestational trophoblastic disease is a spectrum of pregnancy disorder arising from the placental trophoblastic tissues. It characterised by the secretion of a distinct tumour marker, the beta-*HCG*. This condition is highly curable even in the presence of metastasis. The incidence of this disease is higher in the Asian population. The major well-established risk factors for gestational trophoblastic disease are advanced maternal age and a past history of gestational trophoblastic disease. Common clinical presentations include vaginal bleeding in early trimester, uterus larger than gestational age, absence of fetal parts after 20 weeks of gestation. Ultrasonography is a reliable non-invasive tool for diagnosis of gestational trophoblastic disease in the clinical setting. All placental tissue following miscarriage or curettage should have histopathological evaluation to exclude gestational trophoblastic disease. Since this group of disorders is one of the highly curable neoplasms, early diagnosis and prompt treatment is necessary.

**Key Words:** Gestational trophoblastic disease, Hydatidiform mole, Beta-*HCG*

## Introduction

Gestational trophoblastic disease is a heterogeneous group of neoplastic disorders, which originate from the placental trophoblastic epithelium. This group of diseases can occur following both normal and abnormal fertilisation. Gestational trophoblastic disease comprises a wide spectrum of conditions, which may vary in their clinical presentations, malignant potential and outcomes. Under the WHO classification, gestational trophoblastic disease includes hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumour and miscellaneous and unclassified trophoblastic lesions<sup>1</sup>. The characteristic feature of gestational trophoblastic disease is that this group of disorders secrete high level of a distinct tumour marker, the beta-subunit of human chorionic gonadotrophin, better known as  $\beta$ -*HCG*. Another unique feature of gestational trophoblastic

disease is their ability to be cured even in the presence of widespread metastasis<sup>1,2,3</sup>.

## Pathology and cytogenic features

A complete hydatidiform mole often has the classical features of bunch of grapes appearance due to the enlarging trophoblastic villi, which forms the transparent vesicles. It is often bulky containing bloody tissue without any normal placental tissue or embryo. Cytogenetic analysis of complete mole shows 46 XX karyotype with both sets of chromosomes being of paternal origin. Most of 'complete moles' result from the fertilisation of an anuclear ovum by a haploid 23X paternal sperm which subsequently undergoes duplication. Less than 10% of complete moles are due to fertilization of an empty ovum by 2 haploid sperms resulting in 46 XX or 46 XY karyotype<sup>2,3</sup>.

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In partial moles two populations of villi are present, one with normal morphology and the other with scattered hydropic villi and trophoblastic hyperplasia. Fetal vessels are usually present histologically. A fetus may be present in partial mole. Partial mole occurs when an ovum with 23X chromosomes is fertilised by two sperms that carry either of the sex chromosomes, resulting in chromosomes configuration of XXX, XXY or XYY (triploidy). If a fetus is present with a partial mole, it is usually unhealthy with multiple congenital malformations and intrauterine growth retardation<sup>2,3</sup>. An invasive mole is a form of gestational trophoblastic disease characterised by the presence of enlarged villi, which penetrates deeply into myometrium, it may also extend into the broad ligament or metastasize to the lungs. Histologically, invasive mole is characterised by hyperplasia of cytotrophoblastic and syncytial elements and the persistence of the villi. Invasive mole is distinguishable from choriocarcinoma by the presence of villi and it can regress spontaneously<sup>1</sup>.

### Epidemiology

The incidence of gestational trophoblastic disease varies greatly in different parts of the world. The reported incidence based on hospital studies and survey in Europe and North America varies from 66-121 per 100,000 pregnancies<sup>2</sup>, but the incidence of this disease in Asia seems to be higher. In Japan the reported incidence is about 2 per 1000 pregnancies and in Taiwan the reported incidence is 1 in 125 pregnancies. In Singapore the incidence is about 115 per 100,000 deliveries<sup>1,2</sup>. The high incidence of molar pregnancy in some populations has been attributed to nutritional and socioeconomic factors. It was reported that regions with a high incidence of molar pregnancy correspond to the geographic areas with a high frequency of vitamin A deficiency<sup>2</sup>. Variations in the worldwide incidence rates of molar pregnancy may also be result of discrepancies between population-based and hospital-based data<sup>2</sup>.

In Malaysia, the incidence of molar pregnancy is about 2.8 per 1000 deliveries and the incidence of gestational trophoblastic neoplasm is about 1.59 per 1000 deliveries. This problem is reported to be more common among the Chinese as compared to Malays and Indians<sup>7</sup>.

### Risk factors

The major risk factor for developing GTD is advanced maternal age. A maternal age above 35 years has

consistently proven to be a risk factor for a complete mole. The postulated hypothesis is that the ova from the older women may be more susceptible to abnormal fertilization<sup>2</sup>. Overall it was found that across all studies of different type of GTD, mothers over the age of 40 have 5-10 times greater chances of GTD<sup>2,4</sup>. The second most important risk factor is previous history of GTD. It is documented that the risk of another hydatidiform mole in subsequent pregnancy is about 1% and the risk increases to 25% in mothers who have more than one past history of hydatidiform mole. A previous history of hydatidiform mole also has been associated with 1000-2000 times increased risk of choriocarcinoma<sup>1,2</sup>. An increased risk is evident for hydatidiform mole for women with blood group A and men with group O or A as compared with all other combinations with a relative risk of 1.1-2.8<sup>1</sup>. The use of oral contraceptive pills is generally associated with increased risk 1.1-2.6%<sup>1</sup>. Dietary factors such as beta-carotene intake has been suggested in some studies in Italy as being a protective factor, however subsequent studies did not confirm similar findings<sup>1</sup>.

### Clinical manifestation

The most common presentation of a complete molar pregnancy is vaginal bleeding in first trimester, which mimics those of a miscarriage, which occurs up to 90% of patients. Because the bleeding is prolonged, more than 50% of patients will have symptoms of anaemia<sup>2,5</sup>. Uterus size bigger than the gestational age occurs in more than 50% of the patients especially in a case of complete molar pregnancy. Other systemic features suggestive of molar pregnancy are hyperemesis gravidarum, preeclampsia before 20 weeks and sign and symptoms of hyperthyroidism in about 7% of the patients<sup>5</sup>. Theca-lutein ovarian cyst was reported in 20-40 percent of the patients resulting from ovarian hyperstimulation by human chorionic gonadotropin. Respiratory distress occurs in about 2% of the patients resulted from cardiopulmonary complications such as trophoblastic emboli phenomenon, preeclampsia and thyroid toxic crisis<sup>5</sup>. A minority of patients may have history of passing out mucus and vesicles. Patients with partial moles generally have fewer symptoms. In general they present with signs and symptoms of incomplete or missed miscarriage. Among those with symptoms, the commonest presentation is still per vaginal bleeding. Preeclampsia and uterine size larger than gestational age is less frequent. The diagnosis of partial mole is usually made from histopathological examination of the products of conception following a curettage procedure<sup>3,4,5</sup>.

### Investigation and diagnosis

Ultrasonography is a sensitive non-invasive investigation for the diagnosis of gestational trophoblastic disease. Complete hydatidiform mole exhibits a characteristic finding known as "snowstorm" appearance due to the diffuse hydropic swelling and vesicles formation of the villi. (Figure 1) Ultrasonography is indicated when a pregnant mother presents with early trimester bleeding, uterus larger than gestational age and absent of fetal movement or fetal parts on examination after 20 weeks. In partial mole, ultrasonography will demonstrate focal cystic spaces within the placenta and increase in the transverse diameter of the gestational sac. It was reported that when these two features are present, the positive predictive value in diagnosing a partial mole is 90%<sup>2</sup>.

Quantitative assessment of serum  $\beta$ -HCG is very important. The level is typically in excess of 100,000 mIU/ml in a complete mole. A partial mole may have the  $\beta$ -HCG levels in high to normal range. Urine HCG in dilution is an alternative investigation if serum  $\beta$ -HCG is not available but it is less sensitive and qualitative. In rare occasions, false positive result of elevated serum  $\beta$ -HCG occurs in a normal person due to the presence of heterophilic antibodies. Absence of  $\beta$ -HCG in concurrent urine sample or absence of decreased  $\beta$ -HCG following serum sample dilution is diagnostic of a false positive result<sup>6</sup>.

Other laboratory investigations necessary for patient assessment include: haemoglobin level to assess the patient's anaemic status, platelet count as the development of coagulopathy such as DIVC is a known complication, liver function test to exclude metastasis and renal function test for assessment of patient's electrolyte and hydrational status. Serum thyroxine level is indicated if signs and symptoms of hyperthyroidism are present. Base-line chest radiograph should be taken because the lungs are a primary site of metastasis for malignant trophoblastic tumours.

### Treatment

After the diagnosis of molar pregnancy is made and the patient has undergone full evaluation, evacuation of the uterus is always necessary. Suction curettage is the method of choice. Medical termination such as the use of per-vaginal prostaglandin should be avoided because of the risk of embolisation and dissemination of trophoblastic tissue through the venous system<sup>9</sup>. Where possible oxytocin infusion is commenced after

suction evacuation is complete to reduce the possibility of haemorrhage<sup>5,9</sup>. Trophoblastic tissues express the RhD factor, therefore mothers who are RhD-negative should receive Rh immunoglobulin at the time of evacuation<sup>5,9</sup>.

### Post evacuation management

Up to 20% of patients with complete mole and 5% of patients with partial mole present with residual disease, therefore close follow up and monitoring is mandatory after suction curettage. Serial quantitative  $\beta$ -HCG levels should be determined during follow up. The level is monitored weekly until it is undetectable for 3 consecutive weeks then followed by monthly monitoring until undetectable for six consecutive months. Levels of beta HCG should consistently drop and should never increase<sup>5,6</sup>. The average time to the first undetected level of beta HCG following evacuation is about 9-11 weeks (Figure 2). Any rise in levels should prompt a pelvic examination and further evaluation for persistent of the disease or metastasis.

Contraception is recommended during the entire period of follow-up following evacuation of the molar pregnancy for 6 months to a year. The reasons being that if pregnancy occurs during this time, the increased  $\beta$ -HCG makes detection of persistent molar disease difficult. Women should not get pregnant till  $\beta$ -HCG levels have been normal for six months<sup>9</sup>. Intrauterine contraceptive devices should not be used because of the risk of uterine perforation if invasive mole is present; it is also a cause of vaginal bleeding which can be misleading. Increased incidence of persistent molar pregnancy has been reported in patients taking oral contraceptive pills (OCP) before the  $\beta$ -HCG levels normalised, therefore OCP is best avoided. Surgical sterilization is suitable for those who have achieved desired family size, otherwise barrier methods would be the best choice of contraception. Any future pregnancies must have early booking and evaluation because patients with a complete mole have 10-fold risk or 1 in 55 of molar pregnancy in subsequent pregnancies<sup>5,6,9</sup>.

### Persistent Gestational Trophoblastic Disease

Persistent gestational trophoblastic disease is diagnosed when the levels of serum  $\beta$ -HCG plateau or rises during the 3 consecutive weeks following evacuation of the molar tissue or the levels persistent above 20,000 mIU/ml. The incidence of persistent gestational

trophoblastic disease is 20% following a complete mole and about 2-4% following partial mole. This entity can manifest as locally invasive or metastatic lesions. The metastatic type can be categorised into those with good and poor prognosis, depending on how long the disease is present, pre-treatment  $\beta$ -HCG level, location of spread and patient's respond to chemotherapy. Common sites of metastasis are lungs (80%), vagina (30%), pelvis (20%), brain (10%) and liver (10%)<sup>6</sup>. Patients with chest metastasis will present with cough, haemoptysis or signs of pulmonary hypertension.

The prognostic factors scoring system (Table 2) is proposed by the World Health Organisation (WHO), it can reliably predict the potential for resistance to chemotherapy<sup>2</sup>. This prognostic indicators should be

part of the evaluation by any physician who follow up the patients.

Women with the scoring <6 (low risk) are administered methotrexate. Women who are resistant to methotrexate are treated with intravenous Actinomycin D and Etoposide. Women scoring >7 (high risk) will receive combination chemotherapy: intravenous etoposide, Methotrexate and Actinomycin D, Vincristine and cyclophosphomide (EMACO regime).

Overall complete remission is documented in about 75% of patients treated with multi-agent chemotherapy<sup>6,8</sup>. If brain metastasis is detected, then local radiation therapy is indicated. Hysterectomy can be performed in those patients in whom the tumour is resistant to treatment<sup>6</sup>.

**Table I: Differences Between a Complete Mole and a Partial Mole**

Characteristics	Complete Mole	Partial Mole
Hydatidiform swelling of the villi	Generalised and diffuse edema	Focal and varying-sized
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Fetal tissue	Absent	Present
Karyotyping	Diploid, Paternal origin (46 XX or 46 XY)	Triploid Maternal/Paternal Triploid (69 XXY, XXX, XYY)

**Table II: International Federation of Gynecology and Obstetrics (FIGO) Staging for Gestational Trophoblastic Tumours**

Stage	Criteria
I	Disease confined to the uterine corpus
A	No risk factors
B	One risk factors
C	Two risk factors
II	Metastatic disease to the vagina/pelvis
A	No risk factors
B	One risk factor
C	Two risk factors
III	Metastatic disease to the lungs
A	No risk factors
B	One risk factors
C	Two risk factors
IV	Distant metastatic sites
A	No risk factors
B	One risk factor
C	Two risk factors
Risk Factors	hCG>100,000 mIU/mL Interval >6 months between antecedent pregnancy and treatment

Source: FIGO

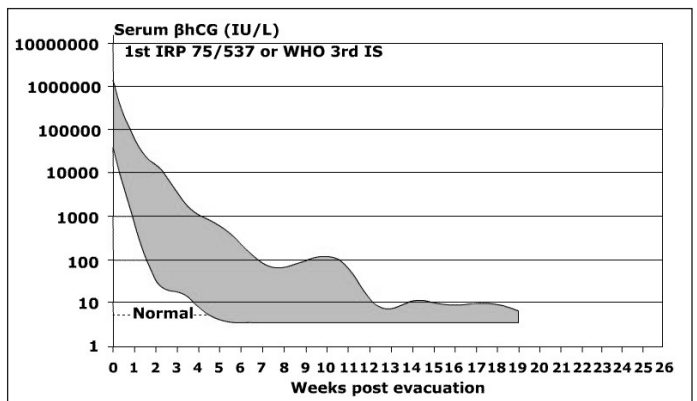
**Table III: Scoring System for Determining Resistance to Chemotherapy**  
**Low Risk: Total Score 4 or less      Moderate Risk: 5-7      High Risk: >7**

Prognostic Factor	Score			
	0	1	2	4
Age	≤39	>39		
Antecedent pregnancy	Mole	Abortion	Term	
Interval between end of antecedent pregnancy and start of chemotherapy (month)	<4	4-6	7-12	>12
Human chorionic gonadotropin (IU/l)	<10 <sup>3</sup>	10 <sup>3</sup> -10 <sup>4</sup>	10 <sup>4</sup> -10 <sup>5</sup>	>10 <sup>5</sup>
ABO group (female, male)		O,A or A,O	B,AB	
Largest tumour (cm)		3-5	>5	
Metastasis				
Site		Spleen, kidney	GIT, liver	Brain
No. identified		1-3	4-8	>8
Prior Chemotherapy			1 drug	≥2 drugs

Source: World Health Organisation



**Fig. 1: Ultrasonography of hydatidiform mole showing multiple vesicles appearance without a fetus**



**Fig. 2: Serum Beta HCG regression curve**

**Conclusion**

Gestational trophoblastic disease remains an important disorder of early pregnancy. This disease has high frequencies in some parts of Asia. Advanced maternal age and past history of gestational trophoblastic disease are well known risk factors. Clinical manifestations of this disease depends on the type of trophoblastic disease. Persistent trophoblastic disease causes local

invasion and also distant metastasis. This group of disorder is one of the highly curable neoplasms, therefore early diagnosis and prompt treatment is necessary. Physician managing mothers in early pregnancy should be alert of the diagnosis of gestational trophoblastic disease if the mother presents with history of vaginal bleeding, uterus larger than dates, absent of fetal movements after 20 weeks and past history of molar pregnancy.

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## Gestational Trophoblastic Disease

### Multiple Choice Questions (MCQ)

1. The following are recognized risk factors for gestational trophoblastic disease:
  - A. Primigravida
  - B. Elderly pregnancy
  - C. Past history of molar pregnancy
  - D. Blood group A
  - E. Early menarche
  
2. The following are clinical features of a molar pregnancy:
  - A. Early trimester per vagina bleeding
  - B. Uterus larger than gestational age
  - C. Severe hyperemesis gravidarum
  - D. Presence of ovarian mass
  - E. Dyspnoea
  
3. The following are pathological features of a complete mole:
  - A. Generalised diffuse hydropic swelling of the villi
  - B. Focal trophoblastic hyperplasia
  - C. Presence of fetal vessels
  - D. Diploid karyotyping
  - E. Scalloping of villi
  
4. The following are recognized complications of molar pregnancy:
  - A. Disseminated intravascular coagulopathy
  - B. Pulmonary metastasis
  - C. Hypovolumic shock
  - D. Pre-eclampsia
  - E. Diabetes mellitus
  
5. The following are recommended management plan for gestational trophoblastic disease:
  - A. Pre-vaginal prostin induction
  - B. Serial quantitative  $\beta$ -HCG monitoring until the levels are undetectable.
  - C. Women with low risk scoring benefit from single drug methotrexate treatment in persistent mole.
  - D. Use of oral contraceptive pills as the first choice for contraception.
  - E. Early antenatal booking for all future pregnancies.