

# **Gestational Trophoblastic Disease in 2005**

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*Gestational trophoblastic diseases are still problematic in our practice. Even the incidence is in generally decreasing. And the development of Medicine in this decade can elucidate some parts of pathophysiology at cellular and molecular levels. However, malignant changes still can not be prevented. Approximately 20% of patients will develop malignant sequelae requiring administration of chemotherapy after evacuation of hydatidiform moles<sup>(1)</sup>. Most patients with postmolar gestational trophoblastic disease will have non-metastatic molar proliferation or invasive moles, but gestational choriocarcinomas and metastatic disease can develop in this setting. Gestational choriocarcinoma occurs approximately 50% after term pregnancies, 25% after molar pregnancies, and the remainder after other gestational events<sup>2</sup>. Although much rarer than hydatidiform moles or gestational choriocarcinomas, placental site trophoblastic tumors can develop after any type of pregnancy<sup>3</sup>. For optimal management, practicing obstetrician-gynecologists should be able to diagnose and manage primary molar pregnancies, diagnose and stage malignant gestational trophoblastic neoplasia, and assess risk in women with malignant gestational trophoblastic neoplasia. This chapter views some points which may be useful for evidence-based practice in modern Medicine.*

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With increasing understanding of the biological evolution of GTD the terms 'benign' and 'malignant' for hydatidiform mole (HM) and persistent GTD are probably best avoided. The term gestational trophoblastic tumour (GTT) has been applied to persistent GTD - but particularly to invasive mole and choriocarcinoma. Most recently it has been suggested that the term gestational trophoblastic neoplasia (GTN) should be used for all persistent GTD.

### **The statistics for gestational trophoblastic disease<sup>(2)</sup>**

The epidemiology of GTD is not clear. Problems arise in methods of data collection, bias, interpretation and differing means of expressing incidences. It would appear that there is a genetic basis for the genesis and implantation of HM, the exact nature of which remains to be determined. Whether there is a genetic basis for the development of GTN remains to be elicited. Gestational trophoblastic diseases account for less than 1% of female reproductive system cancers. Hydatidiform moles occur in approximately 1 pregnancy out of 300-1,000 in Asian countries. In very rare cases (less than 1%), a normal fetus can develop along with the hydatidiform mole. In about 10% to 20% of cases, a hydatidiform mole can progress

to become an invasive mole or persistent gestational trophoblastic disease (GTD). Overall, invasive moles occur at an estimated rate of 1 pregnancy in 15,000. Choriocarcinoma, a malignant form of GTD, is even less common, affecting up to 1 pregnancy out of 2,500 to 20,000 in many Asian and African countries. About 1% to 3% of hydatidiform moles progress to become choriocarcinoma. About half of all choriocarcinomas and persistent GTN, however, do not start off as moles. Approximately 25% of all choriocarcinomas develop in women who have a miscarriage (spontaneous abortion), intentional abortion, or tubal pregnancy (development of the fetus in the fallopian tube, rather than in the uterus). Another 25% occur after normal pregnancy. Nearly 100% of women with GTD who do not have certain complicating factors – in other words, those with a good prognosis can be cured.

### **Management after evacuation of hydatidiform mole**

As long as hCG values are decreasing after molar evacuation, there is no role for chemotherapy. Repeat curettage is not recommended because it does not often induce remission or influence treatment and may result in uterine perforation and hemorrhage<sup>(4)</sup>. Second uterine evacuation can be a useful therapeutic

option for patients with presumed persistent GTD. After second evacuation, 68% completed the follow-up programme without further evidence of persistent disease or need chemotherapy<sup>(4)</sup>. A new intrauterine pregnancy should be ruled out on the basis of hCG levels and ultrasonography, especially when there has been a long delay in follow-up of serial hCG levels and noncompliance with contraception. Pregnancy obscures the value of monitoring hCG levels during this interval and may result in a delayed diagnosis of postmolar malignant gestational trophoblastic disease.

### Criteria for treatment of post-molar GTN

A variety of hCG criteria have been used to diagnose postmolar gestational trophoblastic disease<sup>(5-7)</sup>. Recently, the International Federation of Gynecologists and Obstetricians (FIGO) standardized hCG criteria for the diagnosis of postmolar gestational trophoblastic disease<sup>(6)</sup>. Based on consensus committee recommendations from the Society of Gynecologic Oncology, the International Society for the Study of Trophoblastic Disease, and the International Gynecologic Cancer Society, the following criteria were proposed by FIGO<sup>(8)</sup>:

1. An hCG level plateau of four values  $\pm 10\%$  recorded over a 3-week duration (days 1, 7, 14, and 21)
2. An hCG level increase of more than 10% of three values recorded over a 2-week duration (days 1, 7, and 14)
3. Persistence of detectable hCG for more than 6 months after molar evacuation.
4. The histologic diagnosis of choriocarcinoma or invasive mole from findings from uterine curettage, or the identification of clinical or radiographic evidence of metastases.

In the USA have favoured early treatment for suspected cases of persistent GTD, so that if human chorionic gonadotrophin (hCG) levels increase over 2 weeks or plateau over a period of 3 or more weeks, immediate workup and chemotherapy for post-molar GTD. In the UK and certain other centers a more conservative approach was possible with a meticulous surveillance, without detriment to the overall cure rate. What are the characteristics of false-positive hCG values, also known as “phantom hCG”?

Rarely, women have persistently elevated hCG levels but are subsequently found to have a false-positive hCG assay result, sometimes after receiving chemotherapy or surgery for presumed malignant gestational trophoblastic disease. Most patients with false-positive hCG values have low-level hCG eleva-

tions<sup>(9-11)</sup>, but values higher than 300 mIU/ml have occasionally been recorded. False-positive hCG values result from interference with the hCG immunometric sandwich assays, most often caused by non-specific heterophilic antibodies in the patient's serum<sup>(9)</sup>. Many of these patients have an undefined previous pregnancy event and do not have radiographic evidence of metastatic disease.

False-positive hCG values may also appear after evacuation of a hydatidiform mole or following a clearly defined pregnancy event, such as an ectopic pregnancy, and a urine pregnancy test may be considered to differentiate between the two<sup>(12)</sup>. False-positive test results should be suspected if hCG values plateau at relatively low levels and do not respond to therapeutic maneuvers, such as methotrexate given for a presumed persistent mole or ectopic pregnancy. Evaluation should include evaluation of serum hCG levels using a variety of assay techniques at different dilutions of patient serum, combined with a urinary hCG level if the serum level is higher than the threshold for the urinary assay, usually more than 50–60 mIU/ml<sup>(9-11)</sup>. False-positive hCG assays will usually not be affected by serial dilution of patient sera and will have marked variability using different assay techniques, with most assays reflecting undetectable hCG levels<sup>(9,11)</sup>. Heterophilic antibodies are not excreted in the urine; therefore, urinary hCG values will not be detectable if they are the cause of serum hCG level elevation<sup>(9)</sup>. Other techniques are also available to inactivate or strip the patient's serum of heterophilic antibodies. It is important to exclude the possibility of false-positive hCG values before subjecting these patients to hysterectomy or chemotherapy for gestational trophoblastic neoplasia.

### Staging and classification of gestational trophoblastic disease<sup>(13-14)</sup>

Many staging, classification and prognostic systems have been applied. Also terminology has differed across the world, together with criteria for treatment. Consequently it has been difficult to compare results from different centers and it is likely that some patients have been either under or over-treated, resulting in increased chemoresistance or treatment toxicity, respectively. This need to analyses for further confirmation of what is a well recognized feature of persistent GTD. Modifications in the FIGO staging and WHO scoring systems were suggested and this was approved by the Council of FIGO2000. Staging should be based on history, clinical examination, and appro-

ropriate laboratory and radiological studies. Since hCG and b-hCG titers accurately reflect clinical disease, histologic verification is not required for diagnosis, although it may aid in therapy. Risk factors affecting staging include the following:

1. Urinary hCG >100000 mIU/ml (or serum b-hCG >40000 mIU/ml).

2. Duration of disease >6 months from termination of the antecedent pregnancy.

The following factors should be considered and noted in reporting:

1. Prior chemotherapy for known GTD
2. Placental site tumors should be reported separately
3. Histologic verification of disease is not required

Traditionally the WHO scoring system is divided into low, medium and high risk groups. It is suggested that clinical decisions should be based on two groups: low risk  $\leq 6$  intimating single agent chemotherapy, and high risk, mandating multi-agent chemotherapy. There will always be a slightly grey area between low and high risk. However, provided clinicians are confident if they start a patient on low risk treatment that resistance can be easily salvaged with multi-agent chemotherapy then the outcome should be satisfactory since any mortality in this disease is associated with higher scores rather than those in the borderline zone between low and high. Some patients will be spared the more aggressive chemotherapy regimens with consequent reduction in early and late toxicity. Of note is that classification does not take account of molar pregnancy not progressing to GTN, that placen-

tal site trophoblastic tumour will be categorized separately and that chest X-ray will still be used in the risk scoring of chest metastases.

### How is low-risk metastatic gestational trophoblastic disease treated? <sup>(15-17)</sup>

Patients with metastatic gestational trophoblastic disease who lack any of the clinical high-risk factors or have a FIGO risk score less than 7 <sup>(5)</sup> have low-risk disease. They can be treated successfully with initial single-agent regimens. Most often, this consists of 5-day treatment using methotrexate or intravenous dactinomycin recycled at 14-day intervals. Approximately 40% of these patients will require alternative therapy to achieve remission; however, essentially all patients with low-risk metastatic gestational trophoblastic disease can be cured with conventional chemotherapy. Hysterectomy in conjunction with chemotherapy may also decrease the amount of chemotherapy required to achieve remission in these patients <sup>(16,18)</sup>. Similar to the treatment of women with nonmetastatic gestational trophoblastic disease, 1–2 cycles of chemotherapy should be given after the first normal hCG level. Recurrence rates are less than 5% among patients successfully treated for low-risk metastatic disease <sup>(19)</sup>.

### How is high-risk metastatic gestational trophoblastic disease treated?

Patients with one or more of the clinical classification system risk factors or a FIGO risk score of 7 or higher or stage IV have high-risk disease. They should be treated more aggressively with initial combi-

A. Staging				
Stage I	Disease confined to the uterus.			
Stage II	GTN extends outside the uterus, but is limited to the genital structures. (adnexa, vagina, broad ligament).			
Stage III	GTN extends to the lungs, with or without known genital tract involvement.			
Stage IV	All other metastatic sites.			
B. Scoring				
	0	1	2	4
Age (years)	<40	$\geq 40$	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4–<7	7–<13	$\geq 13$
Pre-treatment serum hCG (IU/ml)	$<10^3$	$10^3$ – $<10^4$	$10^4$ – $<10^5$	$\geq 10^5$
Largest tumour size(cm) (including uterus)	<3	3–<5	$\geq 5$	–
Site of metastasis	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

nation chemotherapy with or without adjuvant radiotherapy or surgery to achieve a cure rate of 80%–90%<sup>(20)</sup>. In contrast to the treatment of patients with nonmetastatic or low-risk metastatic gestational trophoblastic disease, early hysterectomy does not appear to improve the outcome in women with high-risk metastatic disease<sup>(16)</sup>. Despite this success of chemotherapy in inducing clinical complete responses in most patients with gestational trophoblastic neoplasia, approximately 25% of high-risk patients will have an incomplete response to first-line sequential single-agent or multi-agent chemotherapy, respectively, or will relapse from remission. Secondary chemotherapy which has been reported, consisted mainly of platinum-etoposide combinations with methotrexate and actinomycin D (EMA-EP), bleomycin, platinum (BEP), or ifosfamide (VIP, ICE). Adjuvant surgery and radiotherapy were used in selected patients<sup>(21)</sup>. Chemotherapy is continued until hCG values have normalized, followed by at least two or three courses of maintenance chemotherapy in the hopes of eradicating all viable tumors. Despite the use of sensitive hCG assays and maintenance chemotherapy, up to 13% of patients with high-risk disease will develop recurrence after achieving an initial remission. Patients should be counseled to use a reliable form of hormonal contraception during the first year of remission. There does not appear to be an increase in the risk of congenital malformations or other complications related to pregnancy. Outcome of Pregnancies Occurring before Completion of Human Chorionic Gonadotropin Follow-Up in Patients with Persistent Gestational Trophoblastic Tumor<sup>(22)</sup>

Retrospective record review of patients with gestational trophoblastic tumor who conceived before standard hCG follow-up was completed during 1973–1998 from New England Trophoblastic Disease Center Brigham and Women's Hospital and Dana Farber Cancer Institute, Harvard Medical School. Forty-three patients stage I-III treated for gestational trophoblastic tumors conceived before human chorionic gonadotropin follow-up was completed. The antecedent pregnancy was complete mole and partial mole. The mean interval from human chorionic gonadotropin remission to new pregnancy was 6.3 months (range 1–11 months). Ten patients underwent elective termination and four patients were lost to follow-up. Of the remaining 75.9% had term live births, 10.3% had preterm delivery, 10.3% had spontaneous abortion, and 3.5% had a repeat mole. Two cases of fetal anomalies were detected; one was inherited polydactyly and the other

was hydronephrosis. One patient developed choriocarcinoma with lung involvement and underwent cesarean section at 28 weeks; a normal fetus was delivered and no choriocarcinoma was detected in the placenta.

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