

Management of Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) encompasses a spectrum of interrelated disease processes originating from the placenta. Several terms have been used to refer to these, including GTD, gestational trophoblastic neoplasia, and gestational trophoblastic tumors. The histologically distinct disease entities encompassed by this general terminology include complete and partial hydatidiform moles, invasive moles, placental site trophoblastic tumors (PSTT), and choriocarcinomas. Before the advent of sensitive assays for human chorionic gonadotropin (hCG) and efficacious chemotherapy, morbidity and mortality from all forms of GTD often occurred. However, with currently available quantitative assays for the beta subunit of hCG (b-hCG) for monitoring disease and current approaches to chemotherapy, most women with malignant GTD can be cured and their reproductive function can be preserved.

Estimates of the incidence of various forms of GTD vary. In the United States, hydatidiform moles are observed in approximately 1/600 therapeutic abortions and 1/1,000-1,200 pregnancies (1). Therefore, the practicing obstetrician-gynecologist may see approximately one or two molar pregnancies each year. Approximately 20% of patients with primary hydatidiform mole will develop malignant sequelae; the majority of these will be invasive moles and will not metastasize. Choriocarcinoma occurs in approximately 1/20,000-40,000 pregnancies; approximately 50% of gestational choriocarcinomas develop after term pregnancies, with 25% following molar gestations and 25% following other gestations (1). To allow optimal treatment, the obstetrician-gynecologist should be able to diagnose and manage women with primary molar gestations, diagnose malignant GTD, and assess risk in women with malignant GTD.

Hydatidiform Mole

Classification

Recent studies have defined two different forms of hydatidiform mole: partial and complete molar gestations. They are distinct cytogenetic disease processes with characteristic clinical and histopathologic findings and do not represent a "transition" from normal gestation to hydatidiform mole. The distinctive features of these two entities are outlined in Table 1. However, despite the clinical and pathologic differences, the management of patients with partial and complete moles should be similar.

Partial hydatidiform moles usually have 69 chromosomes derived from two paternal and one maternal haploid sets of chromosomes. Most have a 69,XXX or 69,XXY genotype derived from a haploid ovum with either reduplication of the paternal haploid set from a single sperm, or less frequently, from dispermic fertilization (2). Complete hydatidiform moles usually have a chromosomal complement totally derived from the paternal genome. The 46,XX genotype is most common, representing reduplication of the haploid genome of the sperm and exclusion of the chromosomal complement of the ovum (2). A smaller proportion of complete moles have a 46,XY karyotype consistent with dispermic fertilization.

Malignant sequelae occur in less than 5-10% of patients with partial hydatidiform moles and usually consist of nonmetastatic postmolar GTD (1). The volume and amount of **trophoblastic** proliferation in complete moles generally exceeds that observed in partial moles (2, 3). This proliferation is reflected by the clinical presentation. Initial b-hCG levels are higher than those seen in partial hydatidiform moles. The clinical and sonographic diagnosis is most frequently that of hydatidiform mole, with uterine enlargement beyond the expected gestational age observed in more than 50% of patients with complete moles (3). Patients often present with vaginal bleeding or expulsion of molar vesicles. Medical complications of molar pregnancy, including pregnancy-induced hypertension, hyperthyroidism, anemia, and hyperemesis, are more frequently seen in patients with complete moles (1). Approximately 15-25% of patients with complete moles will have theca lutein cysts of the ovaries with enlargement of greater than 6 cm (4, 5). Approximately 20% will develop malignant sequelae after evacuation of a complete hydatidiform mole (4, 6).

Diagnosis

Hydatidiform moles are usually diagnosed during the first trimester of pregnancy. The most common symptom of a mole is bleeding. Other symptoms include uterine enlargement greater than that expected for gestational dates, absence of fetal heart tones, cystic enlargement of the ovaries, hyperemesis, and an abnormally high serum level of b-hCG. The presence of these symptoms in the first trimester should alert the physician to the possibility of the presence of a mole. Pregnancy-induced hypertension in the first half of pregnancy is virtually diagnostic of hydatidiform mole. Ultrasound has replaced all other means of establishing the diagnosis preoperatively. It typically reveals the absence of a fetus and multiple echogenic areas of villi and clots.

TABLE 1. Features of Partial and Complete Hydatiform Moles

Feature	Partial Mole	Complete Mole
Karyotype	Most commonly 69,XXX or 69,XXY	46,XX or 46,XY
Pathology		
Fetus	Often present	Absent
Amnion, fetal red blood cells	Often present	Absent
Villose edema	Variable, focal	Diffuse
Trophoblastic proliferation	Variable, focal, slight to moderate	Variable, slight to severe
Clinical presentation		
Diagnosis	Missed abortion	Molar gestation
Uterine size	Small for dates	50% are large for dates
Theca lutein cysts	Rare	Occur in 25-30%
Medical complications	Rare	Frequent
Postmolar GTD	< 5-10%	20%

Management

Occasionally, the diagnosis of a hydatidiform mole will be made on the basis of dilation and curettage for an incomplete abortion. In this instance, all patients should have serial determination of quantitative b-hCG levels. A baseline chest X-ray can be considered.

In patients in whom hydatidiform mole is suspected prior to evacuation, the following laboratory studies should be done: complete blood count with platelet determination, clotting function studies, renal and liver function studies, blood type and antibody screen, and determination of b-hCG level. A chest X-ray should also be obtained.

Common medical complications of hydatidiform mole include anemia, infection, hyperthyroidism, pregnancy-induced hypertension, and coagulopathy. As soon as patients with medical complications have been stabilized, the mole should be evacuated. The choice of location for the procedure should be based on the expertise of the physician, uterine size, and existing medical conditions and complications and the ability to manage them at the institution. In most patients, the preferred method of evacuation is suction curettage. Prostaglandins, oxytocin infusion, and hysterotomy are not usually recommended as the sole means of evacuation because they increase blood loss and may increase the risk for malignant sequelae after evacuation compared with suction curettage (4, 7). Furthermore, patients often require curettage after prostaglandins or oxytocin infusions are used to evacuate a mole (7). Evacuation is usually performed under general anesthesia, but local anesthesia may be used in a cooperative patient with a small uterus. After dilation of the cervix, uterine evacuation is accomplished with the largest cannula that can be introduced through the cervix. **Intravenous oxytocin is begun after the cervix is dilated and continued postoperatively for several hours.** After completion of suction curettage, gentle sharp curettage may be performed.

Pulmonary complications are frequently observed around the time of evacuation of hydatidiform mole in patients with marked uterine enlargement. Although the syndrome of **trophoblastic** embolization has been emphasized as an underlying cause for respiratory distress syndrome (8), there are many other potential causes of respiratory distress syndrome in these women. Respiratory distress syndrome can also be caused by high-output congestive heart failure caused by anemia or hyperthyroidism, preeclampsia, or iatrogenic fluid overload (9). In general, these complications should be treated aggressively with therapy directed by Swan-Ganz catheter monitoring and assisted ventilator support as required. Hyperthyroidism and pregnancy-induced hypertension usually abate promptly after evacuation of the molar pregnancy and may not require specific therapy. Theca lutein cysts occur due to b-hCG stimulation and may take several months to resolve after molar evacuation (5).

Hysterectomy is an alternative to suction curettage in selected patients. Usually the adnexa may be preserved. Although hysterectomy reduces the risk of malignant sequelae, the chance of malignant GTD after hysterectomy for hydatidiform mole remains approximately 3-5% (4). Therefore, these patients should be monitored with serial b-hCG levels as follows.

After evacuation, it is important to monitor patients carefully in order to diagnose and treat malignant sequelae promptly. Serial quantitative b-hCG determinations should be performed utilizing radioimmunoassay or a comparable method. Qualitative pregnancy tests should not be used to monitor patients with hydatidiform mole. Examinations are performed to monitor the involution of pelvic structures and to aid in the early detection of metastases. A chest X-ray is indicated if the b-hCG titer rises. **Human chorionic gonadotropin levels should be determined 48 hours after evacuation, every 1-2 weeks until levels are normal, and then at 1-2-month intervals for an additional 6-12 months (4, 6).** Pelvic e Contraception is recommended for at least 6 months to 1 year after remission. The rationale for an interval of monitoring during hCG remission is to allow identification of the rare patients who develop postmolar malignant sequelae after achieving normal hCG values. It should be noted, however, that

virtually all episodes of malignant sequelae occurring after evacuation of a hydatidiform mole occur within approximately 6 months of molar evacuation (4, 6). Therefore, pregnancy after 6-12 months of documented remission of hCG levels minimizes the chance of obscuring a rise in hCG level caused by malignant GTD in this setting. Oral contraceptives do not increase the incidence of postmolar GTD or affect the pattern of regression of hCG levels (10). After completion of surveillance documenting remission, pregnancy can be permitted and hCG monitoring discontinued. Patients with a prior partial or complete molar gestation have a 10-fold increased risk (1-2% incidence) of a second mole in subsequent pregnancies (11). Therefore, all future pregnancies should be evaluated by ultrasound early in their course.

Although prophylactic chemotherapy has been shown to decrease the incidence of postmolar GTD in patients after evacuation of high-risk molar pregnancies, it is not routinely recommended (1). In compliant patients, the low morbidity and mortality achieved by monitoring patients with serial b-hCG determinations and instituting only indicated chemotherapy outweighs the potential risk and small benefit of routine prophylactic chemotherapy. As long as b-hCG values are declining, there does not appear to be any role for chemotherapy. However, if b-hCG values rise or plateau over more than 2 weeks, immediate workup and treatment for malignant postmolar GTD is indicated. Repeat curettage does not often induce remission and may result in uterine perforation (12). If malignant forms of GTD are diagnosed histologically or if patients develop clinical or radiographic evidence of malignant GTD, treatment is indicated (4, 6).

Malignant Gestational Trophoblastic Disease

Histologic Considerations

The clinical presentation of malignant GTD is more important in determining prognosis than the precise histologic diagnosis:

- Invasive moles are characterized by persistence of edematous chorionic villi with **trophoblastic** proliferation invading into the myometrium. They rarely metastasize but are usually treated with chemotherapy.
- Gestational choriocarcinoma is a pure epithelial neoplasm, comprising both neoplastic syncytiotrophoblast and cytotrophoblast elements without chorionic villi. Gestational choriocarcinoma tends to develop early systemic hematogenous metastases, and chemotherapy is indicated.
- Placental site **trophoblastic** tumors are very rare **trophoblastic** neoplasms characterized by absence of chorionic villi and proliferation of intermediate cytotrophoblast cells (13). The dimorphic population of syncytiotrophoblast and cytotrophoblast elements that are observed in choriocarcinoma are lacking in PSTT (13). They secrete amounts of b-hCG that are small in relation to the tumor volume. The PSTT generally are not sensitive to chemotherapy; therefore, it is important to distinguish them histologically from choriocarcinomas. Fortunately, they metastasize very rarely beyond the uterus; hysterectomy is the treatment of choice.

Clinical Diagnosis

Clinically, postmolar GTD is diagnosed on the basis of rising (increase of > 10%) or plateauing (decline of < 10% for at least three values over more than 14 days) b-hCG values. Women with GTD following nonmolar pregnancies may present with subtle signs and symptoms of disease, making a diagnosis difficult. Delayed diagnosis may lead to a worsened outcome. Abnormal bleeding following any pregnancy should be evaluated promptly with b-hCG testing and endometrial sampling to determine the presence of GTD. Metastases from gestational choriocarcinoma have been reported in virtually every body site; thus

this diagnosis should be considered in any postpartum woman presenting with metastatic disease from an unknown primary site. Central nervous system metastases may produce neurologic abnormalities, intracranial hemorrhage, or mass lesions. A serum b-hCG determination and exclusion of normal pregnancy are all that are required to diagnose metastatic GTD in these circumstances.

Once the diagnosis of malignant GTD is suspected or established, immediate evaluation for metastases is mandatory. Along with history and physical examination, the following laboratory studies should be performed: complete blood count with platelet determination, clotting function studies, renal and liver function studies, blood type and antibody screen, and determination of baseline (pretherapy) b-hCG level. Modes of radiographic evaluation that may be used include chest X-ray or computed tomography (CT) scan, pelvic ultrasound, brain CT or magnetic resonance imaging scan, and abdominal-pelvic CT scan or magnetic resonance imaging scan of the liver. Systemic venous metastasis may result in pulmonary or vaginal lesions. Systemic arterial metastasis usually occurs after pulmonary metastases have been established. For a minimum evaluation, a chest X-ray should be performed. If it is positive, CT or magnetic resonance imaging of the brain and abdomen should be performed. However, if the chest radiograph is negative, a CT scan of the chest should be obtained because 40% of patients with negative chest X-rays have metastatic lesions seen on CT scan (14). If the chest CT is positive, the brain and abdomen should be evaluated as previously described.

Classification

Three systems have been proposed for categorization of patients with malignant GTD (1): those developed by the World Health Organization (WHO), the National Institutes of Health (NIH), and the International Federation of Gynecologists and Obstetricians (FIGO). The FIGO system is not clinically useful since it does not take into account other factors which may reflect disease outcome, such as volume of metastatic disease, antecedent pregnancy type, or duration of disease. Therefore, the WHO and NIH systems are used in the United States.

The WHO prognostic index score (Table 2) assigns a weighted value to several individual clinical variables. The total prognostic index score has been shown to correlate with prognosis and response to therapy (15).

The NIH's experience has led to a clinical classification system commonly used in the United States (1, 16, 17) (see the box: Classification of GTD). This system separates patients with nonmetastatic disease from those with metastatic disease, because virtually all patients with nonmetastatic disease can be cured using single-agent chemotherapy. Patients with metastatic GTD are further subdivided. Those with low-risk disease--who lack any clinical risk factors--are likely to respond to single-agent chemotherapy and are considered to have a good prognosis. In contrast, patients with high-risk disease--who have one or more clinical risk factors--are unlikely to respond to single-agent chemotherapy and are, therefore, considered to have a poor prognosis. Patients with a poor prognosis should be treated initially with multiagent chemotherapy.

Although the WHO prognostic index score may provide a more precise definition of prognosis in patients with high-risk disease (15), the NIH clinical classification system allows easy identification of patients with risk factors who are unlikely to respond to single-agent chemotherapy. Virtually all deaths from GTD occur among patients who fall into the poor prognosis, high-risk category (18). All patients identified as having high-risk malignant GTD should be treated in consultation with individuals who are experienced in the therapy of GTD.

Classification of GTD

I. Benign GTD

- A. Complete hydatidiform mole
 - B. Partial hydatidiform mole
- II. Malignant GTD
 - A. Nonmetastatic GTD
 - B. Metastatic GTD
 - 1. Good prognosis, low risk--absence of any risk factor
 - 2. Poor prognosis, high risk--presence of any risk factor
 - a. Duration > 4 months
 - b. Pretherapy level of b-hCG in serum > 40,000 mIU/ml
 - c. Brain or liver metastases
 - d. GTD after term gestation
 - e. Prior failed therapy

Management

Nonmetastatic

The primary remission rates of nonmetastatic GTD are similar, and essentially all patients with this condition ultimately can be cured with chemotherapy. Many chemotherapeutic regimens have been evaluated for the treatment of women with nonmetastatic GTD (see the box: Chemotherapy Regimens for Nonmetastatic GTD). Of the available regimens, the Gynecologic Oncology Group reports that weekly methotrexate is efficacious, minimally toxic, and most cost-effective (19). **Chemotherapy is continued until b-hCG values have achieved normal levels, and then an additional course (two weekly doses) is administered after the first normal hCG value has been recorded. Since methotrexate is excreted entirely by the kidney, patients must have a normal creatinine level prior to each treatment.**

In this group of women, it has been shown that early hysterectomy will shorten the duration and amount of chemotherapy needed to produce remission (20). Therefore, the patient's desire for further fertility should be evaluated at the onset of therapy. Hysterectomy may be performed during the first cycle of chemotherapy. However, continued chemotherapy remains mandatory until hCG values are normal.

Chemotherapy Regimens for Nonmetastatic GTD*

First-line therapy: methotrexate**

- Weekly, 30 mg/m² IM***, or
- Every 2 weeks, a 5-day regimen of 0.4 mg/kg IM (maximum 25 mg/d total), or
- Methotrexate, 1 mg/kg IM, on days 1, 3, 5, and 7 with folinic acid, 0.1 mg/kg IM, on days 2, 4, 6, and 8, or
- Methotrexate, 100 mg/m² IV bolus and 200 mg/m² IV infusion over 12 hours, followed by folinic acid, 15 mg PO every 6 hours for four doses (begun at the end of infusion)

(Alternative therapy: dactinomycin**** or etoposide**)

- Dactinomycin
For 5 days, 9-13 µg/kg IV, every 2 weeks (maximum 500 µg/d), or
Bolus, 1.25 mg/m² IV, every 2 weeks
- Etoposide
For 5 days, 200 mg/m² PO every 12-14 days*****

* Abbreviations: IM = intramuscularly, IV = intravenously, PO = orally.

** Gastrointestinal toxicity is common.

*** A weekly methotrexate regimen is described in Homesley HD, Blessing JA, Rettenmaier M, Capizzi RL, Major FJ, Twiggs LB. Weekly intramuscular methotrexate for nonmetastatic gestational trophoblastic disease. *Obstet Gynecol* 1988;72:413-418

**** Caution: may produce extravasation injury.

***** Universal alopecia results.

Patients whose levels of b-hCG have leveled off or are rising during therapy should be switched to an alternative single-agent regimen. Dosages for dactinomycin and etoposide are shown in the box. The appearance of new metastasis or failure of alternative single-agent therapy mandates the use of multiagent chemotherapy. Hysterectomy should be considered for the treatment of patients with nonmetastatic disease that is refractory to single-agent chemotherapy (20).

Metastatic

Patients with metastatic GTD who lack any of the clinical factors that would suggest a poor prognosis have low-risk disease. They can be treated successfully with single-agent regimens (15, 18, 20). Traditionally, this has consisted of 5-day cycles of single-agent methotrexate or dactinomycin. Approximately 40% of patients will require alternative therapy to achieve remission; however, essentially all patients with low-risk disease can be cured with conventional chemotherapy. Hysterectomy as primary treatment in conjunction with chemotherapy may also decrease the amount of chemotherapy required to achieve remission in these patients (20).

Patients who have one or more high-risk clinical factors according to the NIH classification or who have a WHO prognostic index score greater than 7 have high-risk disease.

These women may require some combination of chemotherapy, radiation, and surgery. Optimal survival in **trophoblastic** disease centers is 60-84% (15, 18, 20, 21). In contrast to findings in patients with nonmetastatic or metastatic, low-risk disease, primary treatment with

hysterectomy does not appear to improve the outcome in patients with metastatic, high-risk disease (20). Initial multiagent chemotherapy is of primary importance. Triple therapy with methotrexate, dactinomycin, and either chlorambucil or cyclophosphamide (MAC) has been the standard regimen for many years in the United States. A multiagent regimen described by Bagshawe has also been used, but any superiority of this more complex regimen over MAC has not been demonstrated (22). With the identification of etoposide as an active agent in the treatment of GTD, a cyclic, non-cross-resistant chemotherapy regimen incorporating etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine (EMA/CO) has been used with a high rate of success in patients with high-risk disease (21).

Management of cerebral and hepatic metastases is controversial. Radiation therapy (2,000 cGy to the liver and 3,000 cGy to the brain) has been used with chemotherapy in an attempt to limit acute hemorrhagic complications from these sites of metastases (18). Although the use of brain irradiation with systemic chemotherapy is successful in controlling metastases (18), a high remission rate has been reported when a modification of the EMA/CO chemotherapeutic regimen was used without brain irradiation (23). Even with intense chemotherapy, additional surgery may be necessary to control bleeding, remove isolated metastases, or treat complications from metastatic disease (20). Chemotherapy is continued until three consecutive normal b-hCG values have been obtained, and this is usually followed by three additional courses of chemotherapy in the hopes of eradicating all viable tumor. Despite using sensitive b-hCG assays and using maintenance chemotherapy, up to 13% of patients with high-risk disease will develop recurrence after achieving an initial remission (17).

Surveillance Following Chemotherapy

After hCG remission has been achieved, patients should be monitored with determinations of b-hCG values at 2-week intervals for the first 3 months of remission and then at 1-month intervals for the first year of remission. The risk of recurrence after one year of remission is less than 1%, but late recurrences have been observed (17). Therefore, it is recommended that patients undergo surveillance of hCG levels at approximately 6-month intervals.

Contraception, preferably with oral contraceptives, should be used during the first year of remission. Pregnancy may be considered after 1 year of remission. Because of the 1-2% risk of a second molar pregnancy in subsequent pregnancies, early ultrasound examination is recommended for all future pregnancies. There does not appear to be an increase in the risk of congenital malformations or complications of pregnancy with subsequent pregnancies.

Summary

Despite the potentially serious outcome of malignant GTD, most women with all forms of GTD can be successfully diagnosed and treated, with preservation of their normal reproductive function. It is important to manage hydatidiform mole properly in order to minimize acute complications, identify malignant sequelae promptly, and begin therapy. It is important to individualize therapy for women with malignant GTD based upon known risk factors, using less toxic therapy for patients with low-risk disease and aggressive multiagent therapy for patients with high-risk disease.