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Diagnosis and Treatment of Gestational Trophoblastic Disease

Gestational trophoblastic disease comprises a spectrum of interrelated conditions originating from the placenta. Other terms often used to refer to these conditions include gestational trophoblastic neoplasia and gestational trophoblastic tumor. Histologically distinct disease entities encompassed by this general terminology include complete and partial hydatidiform moles, invasive moles, gestational choriocarcinomas, and placental site trophoblastic tumors. Before the advent of sensitive assays for human chorionic gonadotropin (hCG) and efficacious chemotherapy, the morbidity and mortality from gestational trophoblastic disease were substantial. At present, with sensitive quantitative assays for β-hCG and current approaches to chemotherapy, most women with malignant gestational trophoblastic disease can be cured and their reproductive function preserved. The purpose of this document is to address current evidence regarding the diagnosis, staging, and management of gestational trophoblastic disease.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology and the SGO Education Committee with the assistance of John Soper, MD, Julian Schink, MD, and David Mutch, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

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Background

Estimates for the incidence of various forms of gestational trophoblastic disease vary. In the United States, hydatidiform moles are observed in approximately 1 in 600 therapeutic abortions and 1 in 1,500 pregnancies (1). Approximately 20% of patients will develop malignant sequelae requiring administration of chemotherapy after evacuation of hydatidiform moles (2, 3). Most patients with postmolar gestational trophoblastic disease will have nonmetastatic molar proliferation or invasive moles, but gestational choriocarcinomas and metastatic disease can develop in this setting. Gestational choriocarcinoma occurs in approximately 1 in 20,000–40,000 pregnancies: approximately 50% after term

pregnancies, 25% after molar pregnancies, and the remainder after other gestational events (4). Although much rarer than hydatidiform moles or gestational choriocarcinomas, placental site trophoblastic tumors can develop after any type of pregnancy (5, 6). To allow optimal management, practicing obstetrician–gynecologists should be able to diagnose and manage primary molar pregnancies, diagnose and stage malignant gestational trophoblastic disease, and assess risk in women with malignant gestational trophoblastic disease to allow referral for appropriate initial treatment. Experience, such as that found at regional gestational trophoblastic disease treatment centers, improves outcomes in the management of malignant gestational trophoblastic disease. Any woman for whom initial therapy for invasive mole has failed or who has a choriocarcinoma diagnosis should be referred to a physician or facility with training, expertise, and experience in managing gestational trophoblastic disease.

Hydatidiform Mole

Classification

Partial and complete hydatidiform moles are distinct disease processes with characteristic cytogenetic, histologic, and clinical features (4). The distinct pathologic features and clinical presentation of these 2 entities are outlined in Table 1. Despite the cytogenetic, pathologic, and clinical differences between the 2 diagnoses, the management of patients with complete and partial moles is similar.

The volume and amount of trophoblastic proliferation in complete moles generally exceed that observed in partial moles and are reflected in the different clinical presentations (see Table 1). The average initial serum hCG levels usually are higher in patients with complete moles than in patients with partial moles (7). Although an increasing proportion of moles are diagnosed as missed abortions on the basis of an early ultrasound examination in the absence of symptoms (8), most patients with complete moles have a clinical or ultrasonographic diagnosis of hydatidiform mole. Uterine enlargement beyond the expected gestational age is observed in up to 50% of patients with complete moles (1). These patients may present with vaginal bleeding or expulsion of molar vesicles. Medical complications of molar pregnancy, including pregnancy-induced hypertension, hyperthyroidism, anemia, and hyperemesis gravidarum, are more frequently seen among patients with complete moles (9). Approximately 15–25% of patients with complete moles will have theca lutein cysts with ovarian enlargement of more than 6 cm (10). Malignant sequelae occur in less than 5% of patients with partial moles, compared with approximately 20% after evacuation of complete hydatidiform moles (see Table 1) (4).

Diagnosis

Hydatidiform moles usually are diagnosed during the first trimester of pregnancy (8, 11). The most common symptom is abnormal bleeding. Other signs and symptoms include uterine enlargement greater than expected for gestational age, absent fetal heart tones, cystic enlargement of the ovaries, hyperemesis gravidarum, and an abnormally high level of hCG for gestational age (4). Presence of these features in the first trimester should

Table 1. Features of Partial and Complete Hydatidiform Moles

Feature	Partial Mole	Complete Mole
Karyotype	Most commonly 69,XXX or 69,XXY	Most commonly 46,XX or 46,XY
Pathology		
Fetus	Often present	Absent
Amnion, fetal red blood cells	Usually present	Absent
Villous edema	Variable, focal	Diffuse
Trophoblastic proliferation	Focal, slight to moderate	Diffuse, slight to severe
Clinical presentation		
Diagnosis	Missed abortion	Molar gestation
Uterine size	Small for gestational age	50% larger for gestational age
Theca lutein cysts	Rare	15–25%
Medical complications	Rare	Less than 25%
Postmolar malignant sequelae	<5%	6–32%

Modified from Soper JT, Lewis JL Jr, Hammond CB. Gestational trophoblastic disease. In: Hoskins WJ, Perez CA, Young RC, editors. Principals and practice of gynecologic oncology, 2nd ed. Philadelphia (PA): Lippincott-Raven; 1997. p. 1040.

alert the clinician to the possibility of a molar gestation. Pregnancy-induced hypertension in the first half of pregnancy, although uncommon, is suggestive of hydatidiform mole. Ultrasonography has replaced all other noninvasive means of establishing the diagnosis (4, 8). Molar tissue typically is identified as a diffuse mixed echogenic pattern replacing the placenta, produced by villi and intrauterine blood clots, but these findings may be subtle or lacking in cases of early complete or partial moles (8, 11).

Management After Evacuation of Hydatidiform Mole

As long as hCG values are decreasing after molar evacuation, there is no role for chemotherapy. However, if hCG levels increase or plateau over several weeks, immediate evaluation and treatment for malignant postmolar gestational trophoblastic disease are indicated. Occasionally, the plateauing or increasing hCG levels are a result of a false-positive laboratory test result caused by heterophilic antibodies cross-reacting with the hCG test. Such false-positive test results, also known as "phantom hCG," are discussed later.

The diagnosis of malignant sequelae as indicated by the need for chemotherapy include the plateau or increase of hCG levels after evacuation of hydatidiform moles as mentioned previously, the histologic diagnosis of choriocarcinoma or invasive mole on the basis of findings from uterine curettage, or identification of clinical or radiographic evidence of metastases. Repeat curettage is not recommended because it does not often induce remission or influence treatment and may result in uterine perforation and hemorrhage (12).

A variety of hCG criteria have been used to diagnose postmolar gestational trophoblastic disease (1–3, 13, 14). Recently, the International Federation of Gynecologists and Obstetricians (FIGO) standardized hCG criteria for the diagnosis of postmolar gestational trophoblastic disease (14). 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 (14):

1. An hCG level plateau of 4 values plus or minus 10% recorded over a 3-week duration (days 1, 7, 14, and 21)
2. An hCG level increase of more than 10% of 3 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

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.

Malignant Gestational Trophoblastic Disease

Histologic Considerations

The clinical presentation of malignant gestational trophoblastic disease is more important in determining treatment and outcome than the precise histologic diagnosis (4). Postmolar gestational trophoblastic disease is only one of many forms of malignant gestational trophoblastic disease; it comprises noninvasive trophoblastic proliferation, invasive moles, and gestational choriocarcinoma. Gestational choriocarcinomas are derived from term pregnancies in one half of cases, with equal portions of the remaining half from histologically normal gestations and hydatidiform moles. The rarest form of malignant gestational trophoblastic disease, placental site trophoblastic tumor, can follow any pregnancy.

The term invasive mole is used to describe disease confined to the uterus and is characterized by the presence of edematous chorionic villi with trophoblastic proliferation that invade directly into the myometrium. Most cases are clinically diagnosed and are not determined histologically. Dilation and curettage (D&C) should be avoided to prevent morbidity and mortality caused by uterine perforation. Gestational choriocarcinoma is a malignancy, comprising both neoplastic syncytiotrophoblast and cytotrophoblast elements without chorionic villi (4). Gestational choriocarcinomas tend to develop early systemic metastasis (the vagina, lung, liver, and brain are the most common sites), and chemotherapy is indicated when it is diagnosed histologically. When indicated, chemotherapy should be initiated in a timely manner to avoid bleeding complications at metastatic sites.

Placental site trophoblastic tumors are relatively rare (5, 6). They are characterized by absence of villi with proliferation of intermediate trophoblast cells. The number of syncytiotrophoblast cells observed is decreased in placental site trophoblastic tumors, with relatively lower levels of hCG secreted by these tumors. Generally, placental site trophoblastic tumors are not as sensitive to chemotherapy as other forms of malignant gestational trophoblastic disease; therefore, it is important to distinguish these tumors histologically (4). Surgery assumes a critical role in the management of placental site trophoblastic tumors (5, 6). Fortunately, most patients have disease confined to the uterus and are cured by hysterectomy.

Clinical Diagnosis of Malignant Gestational Trophoblastic Disease

Postmolar gestational trophoblastic disease is most frequently diagnosed on the basis of increasing or plateauing hCG values. Women with malignant gestational trophoblastic disease following nonmolar pregnancies may have subtle signs and symptoms of disease, which make the diagnosis difficult (15). Abnormal bleeding for more than 6 weeks following any pregnancy should be evaluated with hCG testing to exclude a new pregnancy or gestational trophoblastic disease. Metastases of gestational choriocarcinoma have been reported in virtually every body site, most commonly the vagina, liver, lung, and brain; however, biopsy of these sites is rarely necessary and may cause excessive bleeding. Central nervous system metastases may produce neurologic symptoms, intracranial hemorrhage, or mass lesions. Gestational choriocarcinoma should be considered in any woman of reproductive age with metastatic disease from an unknown primary site (15). A serum hCG determination and exclusion of pregnancy are all that are required to diagnose metastatic gestational trophoblastic disease in these circumstances.

Clinical Considerations and Recommendations

▶ ***How are patients with hydatidiform moles managed?***

With increasing frequency, the diagnosis of complete or partial moles usually is made after performing a D&C for a suspected incomplete spontaneous abortion (8, 11). In these cases, patients should be monitored with serial determinations of quantitative hCG values. A baseline postevacuation chest X-ray should be considered.

For patients in whom hydatidiform moles are suspected before evacuation, the following tests are recommended (4):

- Complete blood count with platelet determination
- Clotting function studies
- Renal and liver function studies
- Blood type with antibody screen
- Determination of hCG level
- Preevacuation chest X-ray

Medical complications of hydatidiform moles are observed in approximately 25% of patients with uterine enlargement of more than 14–16 weeks' gestational size and are seen less frequently among patients with lesser degrees of uterine enlargement (9). Common medical complications include anemia, infection, hyperthyroidism, pregnancy-induced hypertension, and coagulopathy. Women with signs and symptoms of these complications will need more intensive evaluation (ie, thyroid-stimulating hormones and coagulopathy studies). Moles should be evacuated as soon as possible after stabilization of any medical complications.

To manage potential complications of molar evacuation in a woman with a large uterus, consideration should be given to performing the evacuation in a facility with an intensive care unit, a blood bank, and anesthesia services. For most patients, the preferred method of evacuation is suction D&C (1, 9). Medical induction of labor with oxytocin or prostaglandin and hysterotomy are not recommended for evacuation because they increase blood loss and may increase the risk for malignant sequelae when compared with suction D&C (3, 4, 9, 16). Furthermore, patients most often require D&C to complete the evacuation of moles after medical induction of labor (9). Evacuation usually is performed with the patient under general anesthesia, but local or regional anesthesia may be used for a cooperative patient who has a small uterus. After serial dilation of the cervix, uterine evacuation is accomplished with the largest cannula that can be introduced through the cervix. In some cases, ultrasound guidance may facilitate complete evacuation of the uterus. Intravenous oxytocin is administered after the cervix is dilated and is continued for several hours postoperatively. Rh-negative patients should be treated with anti-D immune globulin after the evacuation even though fetal red blood cells should not be present in a complete mole.

Pulmonary complications are frequently observed around the time of molar evacuation among patients with marked uterine enlargement (9, 17, 18). Although the syndrome of trophoblastic embolization (deportation) has been emphasized as an underlying cause of respiratory distress syndrome following molar evacuation, there are many other potential causes of pulmonary complications in these women. Respiratory distress syndrome can be caused by high-output congestive heart failure caused by anemia or hyperthyroidism, preeclampsia, or iatrogenic fluid overload (17, 18). Generally, these complications should be treated aggressively with therapy directed by central venous or Swan-Ganz catheter monitoring and assisted ventilatory support, as required. Hyperthyroidism and pregnancy-induced hypertension usually abate promptly after evacuation of the mole and may not require specific therapy. Theca lutein cysts are associated with hCG stimulation of the ovaries (10). These may take

several months to resolve after molar evacuation but rarely need to be removed. Surgical intervention should be reserved for rupture or torsion, which is rare (10).

Hysterectomy with preservation of the adnexa is an alternative to suction D&C for molar evacuation in selected patients who do not wish to preserve childbearing. Hysterectomy reduces the risk of malignant postmolar sequelae when compared with evacuation by D&C. However, the risk of postmolar gestational trophoblastic disease after hysterectomy remains approximately 3–5%, and these patients should be monitored postoperatively with serial hCG determinations (3, 4).

▶ *How are patients monitored after evacuation of hydatidiform moles, and what are the considerations regarding contraception and future pregnancies?*

After molar evacuation, it is important to monitor all patients carefully to diagnose and treat malignant sequelae promptly. Serial quantitative serum hCG determinations should be performed using commercially available assays capable of detecting β-hCG to baseline values (<5 mIU/mL). Ideally, serum hCG levels should be obtained within 48 hours of evacuation, every 1–2 weeks while elevated, and then at monthly intervals for an additional 6 months (4). Use of reliable hormonal contraception is recommended while hCG values are being monitored. Frequent pelvic examinations are performed while hCG values are elevated to monitor the involution of pelvic structures and to aid in the early identification of vaginal metastases.

The rationale for an interval of monitoring after normalization of the hCG level is to identify patients who develop malignant postmolar gestational trophoblastic disease. Although rare instances of long latent periods have been reported, most episodes of malignant sequelae after hydatidiform moles occur within approximately 6 months of evacuation (2, 3). Although pregnancies after molar evacuation usually are normal gestations, pregnancy obscures the value of monitoring hCG levels during this interval and may result in a delayed diagnosis of postmolar malignant gestational trophoblastic disease.

Oral contraceptives do not increase the incidence of postmolar gestational trophoblastic disease or alter the pattern of regression of hCG values (13, 19). In a randomized study, patients treated with oral contraceptives had one half as many intercurrent pregnancies as those using barrier methods, and the incidence of postmolar trophoblastic disease was lower in patients using oral contraceptives (20). After completion of documented remission for 6–12 months, women who desire pregnancy may discontinue contraception, and hCG monitoring may be discontinued. Patients with prior partial or complete moles have a 10-fold increased risk (1–2% incidence) of a second hydatidiform mole in a subsequent pregnancy (20). Therefore, all future pregnancies should be evaluated by early obstetric ultrasonography.

▶ *Which patients should be considered for prophylactic chemotherapy to reduce the risk of postmolar trophoblastic disease after molar evacuation?*

Two randomized studies have evaluated prophylactic chemotherapy after molar evacuation. In one study, a single course of methotrexate and folinic acid reduced the incidence of postmolar trophoblastic disease from 47.4% to 14.3% (P <.05) in patients with high-risk moles (as defined by hCG levels greater than 100,000 mIU/mL, uterine size greater than gestational age, and ovarian size greater than 6 cm), but the incidence was not reduced in patients with low-risk moles (21). Patients who received prophylactic chemotherapy but developed postmolar trophoblastic disease required more chemotherapy than those who had not been exposed to prophylactic chemotherapy (21). In the second study, a single course of prophylactic dactinomycin was given to patients after evacuation of high-risk moles (22). Postmolar trophoblastic disease occurred in 50% of the control group, compared with 13.8% of the treatment group. In both studies, there were no deaths in the treatment or control groups caused by gestational trophoblastic disease or treatment toxicity (21, 22). However, there are anecdotal cases of fatalities caused by prophylactic chemotherapy (3, 4), and prophylactic chemotherapy does not eliminate the need for postevacuation follow-up. In compliant patients, the low morbidity and mortality achieved by monitoring patients with serial hCG determinations and instituting chemotherapy only in patients with postmolar gestational trophoblastic disease outweighs the potential risk and small benefit of routine prophylactic chemotherapy.

▶ *What are the considerations for a patient with both a hydatidiform mole and a co-existent fetus?*

Co-existence of a fetus with molar changes of the placenta is relatively rare, occurring in 1 in 22,000–100,000 pregnancies (23). Most of the literature covering this entity consists of case reports, small case series, and reviews of cases reported in the literature. Both complete and partial moles with co-existent fetuses have been reported (24). A variety of criteria have been used to evaluate these pregnancies. Many of the reports that antedated the histologic and cytogenetic distinction between

complete and partial moles likely included partial moles and twin gestations with co-existent fetuses and molar gestations. There may be an increased incidence of co-existing mole and fetus related to an increase in multifetal pregnancies associated with ovulation induction, but this may reflect reporting bias (25).

Most of these twin pregnancies are diagnosed antepartum by ultrasound findings of a complex, cystic placental component distinct from the fetoplacental unit (23, 24); however, in a few cases, the diagnosis is not suspected until examination of the placenta following delivery (25). Medical complications of hydatidiform mole with a co-existent fetus appear to be increased and include hyperthyroidism, hemorrhage, and pregnancy-induced hypertension (23, 24, 26).

Compared with singleton hydatidiform moles, twin pregnancies with a fetus and a mole carry an increased risk for postmolar gestational trophoblastic disease, with a higher proportion of patients having metastatic disease and requiring multiagent chemotherapy (23–26). Among patients with co-existent moles and fetuses who continue pregnancy, a subset develops early complications leading to termination of the pregnancy before fetal viability, with a markedly increased risk of postmolar gestational trophoblastic disease, when compared with patients whose pregnancies continue into the third trimester (23, 24). Among 72 patients identified by a national survey of physicians in Japan in 1997, 24 underwent first-trimester evacuation, with 20.8% subsequently developing postmolar gestational trophoblastic disease (26). In comparison, 45.2% of 31 patients who required evacuation during the second trimester and 17.6% of the 17 who gave birth in the third trimester developed postmolar gestational trophoblastic disease. Nine (50%) of the 18 patients with proved complete hydatidiform moles in association with a fetus subsequently were treated for postmolar gestational trophoblastic disease (26), but it is not certain whether this increased risk resulted from selection bias. Major congenital abnormalities have not been reported in surviving infants.

For patients with co-existing hydatidiform moles and fetuses suspected on the basis of ultrasound findings, there are no clear guidelines for management. The ultrasound examination should be repeated to exclude retroplacental hematoma, other placental abnormalities, or degenerating myoma and to fully evaluate the fetoplacental unit for evidence of a partial mole or gross fetal malformations. If the diagnosis is still suspected and continuation of the pregnancy is desired, fetal karyotype should be obtained, a chest X-ray performed to screen for metastases, and serial serum hCG values monitored. These patients are at an increased risk for medical complications of pregnancy requiring evacuation, including bleeding, preterm labor, and pregnancy-induced hypertension. They should be counseled about these risks and the increased risk of postmolar trophoblastic disease after evacuation or delivery. If the fetal karyotype is normal, major fetal malformations are excluded by ultrasound examination, and there is no evidence of metastatic disease, it is reasonable to allow the pregnancy to continue unless pregnancy-related complications force delivery. After delivery, the placenta should be histologically evaluated and the patient followed closely with serial hCG values, similar to management of a woman with a singleton hydatidiform mole.

▶ *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 elevations (27–29), but occasionally values higher than 300 mIU/mL have been recorded. False-positive hCG values result from interference with the hCG immunometric sandwich assays, most often caused by nonspecific heterophilic antibodies in the patient's sera (27). Many of these patients have an undefined previous pregnancy event and do not have radiographic evidence of metastatic disease.

False-positive hCG values also may 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 (30). 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 (27–29). False-positive hCG assays usually will 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 (27, 29). 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 (27). Other techniques also are 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 disease.

▶ *How are patients with malignant gestational trophoblastic disease classified and staged?*

Three systems have been used to categorize patients with malignant gestational trophoblastic disease: 1) the World Health Organization (WHO) prognostic index score, 2) the Clinical Classification system developed from early experience with chemotherapy for patients treated at the National Institutes of Health (NIH), and 3) the FIGO staging system, which was revised in 2000. The original anatomic FIGO staging system did not take into account other factors that might reflect disease outcome, such as hCG level, duration of disease, or type of antecedent pregnancy (14). The revised FIGO staging system includes a modification of the WHO prognostic index score for risk assessment (Table 2). All systems correlate with clinical outcomes of patients treated for malignant gestational trophoblastic disease and identify patients at risk for failure to respond to chemotherapy (4, 31–33).

The WHO prognostic index score assigned a weighted value to several individual clinical variables (4, 14). The total prognostic index score used a sum of the individual component scores to generate 3 risk categories. The 2000 FIGO modification of the WHO prognostic index score eliminated the determination of patient and consort blood types because these are not uniformly available and consolidated the risk categories into low-risk (total score less than 7) and high-risk (total score of 7 or higher) categories (14). The new FIGO risk index also standardized the radiologic studies to be used for determining the number and size of metastases. In one retrospective analysis, the new FIGO risk index correlated with outcome better than previous modifications of the WHO prognostic index score (32), and several other studies have correlated outcome to WHO prognostic index risk categories (4, 31, 33).

The original analyses of patients treated for metastatic gestational trophoblastic disease at the NIH led to the current Clinical Classification system that is frequently used in the United States (Table 3) (4). This system segregates patients with nonmetastatic disease from those with metastatic disease because virtually all patients with nonmetastatic disease can be cured using initial single-agent chemotherapy, regardless of other risk factors (33, 34). Patients with metastatic disease are further subdivided depending on the presence or absence of factors that correlate with response to initial single-agent chemotherapy (34, 35). Those who lack any of the high-risk clinical factors are likely to respond to initial single-agent therapy and are classified as having good-prognosis metastatic gestational trophoblastic disease. Patients who have any single high-risk clinical factor are classified as having poor-prognosis disease. These patients are not only at an increased risk of failure of single-agent chemotherapy but also have an increased risk of death if treated with single-agent therapy followed by multiagent regimens when compared with patients receiving initial multiagent regimens (35).

Although the WHO prognostic index score may provide a more precise definition of prognosis among patients with high-risk disease, the Clinical Classification system is less complicated and allows easy identification of patients for whom initial single-agent chemotherapy is likely to fail (33). Virtually all deaths from malignant gestational trophoblastic disease occur

Table 2. Revised FIGO Scoring System

FIGO Score	0	1	2	4
Age (y)	≤39	>39	—	—
Antecedent pregnancy	Hydatidiform mole	Abortion	Term pregnancy	—
Interval from index pregnancy (mo)	<4	4–6	7–12	>12
Pretreatment human chorionic gonadotropin level (mIU/mL)	<1,000	1,000–10,000	>10,000–100,000	>100,000
Largest tumor size including uterus (cm)	3–4	5	—	—
Site of metastases	Lung, vagina	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	0	1–4	4–8	>8
Previous failed chemotherapy	—	—	Single drug	2 or more drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. Total score 0–6 = low risk; ≥7 = high risk.

Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and clinical assessment. Int J Gynecol Cancer 2001;11:73–7.

Table 3. Clinical Classification System for Patients With Malignant Gestational Trophoblastic Disease

Category	Criteria
Nonmetastatic gestational trophoblastic disease	No evidence of metastases; not assigned to prognostic category
Metastatic gestational trophoblastic disease	Any extrauterine metastases
Good-prognosis metastatic gestational trophoblastic disease	No risk factors:
	Short duration (<4 mo) Pretherapy hCG level <40,000 mIU/mL
	No brain or liver metastases
	No antecedent term pregnancy
	No prior chemotherapy
Poor-prognosis metastatic gestational trophoblastic disease	Any risk factor:
	Long duration (≥4 mo since last pregnancy)
	Pretherapy hCG level ≥40,000 mIU/mL
	Brain or liver metastases
	Antecedent term pregnancy
	Prior chemotherapy

Abbreviation: hCG, human chorionic gonadotropin.

Soper JT, Lewis JL Jr, Hammond CB. Gestational trophoblastic disease. In: Hoskins WJ, Perez CA, Young RC, editors. Principals and practice of gynecologic oncology, 2nd ed. Philadelphia (PA): Lippincott-Raven; 1997. p. 1055.

among women who fall into the poor-prognosis metastatic disease category, and these patients should be considered to have high-risk disease (33). All patients with high-risk malignant gestational trophoblastic disease should be referred for management in consultation with individuals who are experienced in the treatment of this disease.

▶ *What are the general considerations for the evaluation and treatment of malignant gestational trophoblastic disease?*

Once the diagnosis of malignant gestational trophoblastic disease is suspected or established, immediate evaluation for metastases and risk factors is mandatory. Along with history and physical examinations, the following laboratory studies should be performed: complete blood count with platelet determinations, clotting function studies, renal and liver function studies, blood type and antibody screen, and determination of baseline (pretherapy) hCG level. Recommended radiographic studies include chest X-ray or computerized tomography (CT) scan of the chest, pelvic ultrasonography, brain magnetic resonance imaging or CT scan, and abdominopelvic CT with contrast or magnetic resonance imaging scans (14). Systemic venous metastasis of malignant gestational trophoblastic disease results in pulmonary or occasional vaginal lesions. Systemic arterial metastasis usually occurs only after pulmonary metastases have been established; therefore, the minimum evaluation of a patient with postmolar gestational trophoblastic disease is a chest X-ray. If lung lesions are detected, further imaging of the abdomen and brain should be performed to identify possible liver or brain metastasis.

Because of the relative rarity of malignant gestational trophoblastic disease, there are few randomized trials of therapy, and only one completed trial has been reported to date (13). Most studies have been retrospective analyses of single-institution experiences, but these confirm high activity for a variety of agents in the treatment of malignant gestational trophoblastic disease, including methotrexate, dactinomycin, etoposide, 5-fluorouracil, and cisplatin (4, 36).

▶ *How is nonmetastatic gestational trophoblastic disease treated? In a patient with nonmetastatic gestational trophoblastic disease, which is better: hysterectomy alone or in combination with chemotherapy?*

Primary remission rates of patients treated with a variety of chemotherapy regimens for nonmetastatic gestational trophoblastic disease are similar (4). Essentially all patients with this condition can be cured, usually without hysterectomy. Randomized comparisons of these regimens have not been completed. A prospective phase-II trial by the Gynecologic Oncology Group reported a 70–80% primary remission rate for patients with nonmetastatic gestational trophoblastic disease treated with weekly intramuscular methotrexate at a dose of 30–50 mg/m^2 (37). There was no apparent benefit of increasing the dose to 50 mg/m^2. It was concluded that the weekly methotrexate regimen was the preferred choice of several methotrexate or dactinomycin schedules when efficacy, toxicity, and cost were taken into consideration (37, 38). Chemotherapy is continued until hCG values have reached normal levels; an additional course is administered after the first normal hCG value has been recorded (37, 39). Hematologic indices should be monitored carefully during chemotherapy, but significant hematologic toxicity is infrequent among patients treated with weekly methotrexate (37). Patients should have normal renal and liver functions before each treatment because methotrexate is excreted entirely by the kidney and can produce hepatic toxicity.

In patients with nonmetastatic gestational trophoblastic disease, early hysterectomy will shorten the duration

and amount of chemotherapy required to produce remission (34, 40). Therefore, each patient's desire for future fertility should be evaluated at the onset of treatment. Many experts prefer to perform hysterectomy during the first cycle of chemotherapy and continue administration of chemotherapy for 2 cycles after a negative hCG measurement has been obtained. Chemotherapy after hysterectomy is needed until hCG values become normal.

Patients whose hCG levels reach a plateau or increase during therapy should be switched to an alternative single-agent regimen. If metastases appears or alternative single-agent chemotherapy fails, the patient should be treated with multiagent regimens (4). Hysterectomy should be considered for the treatment of nonmetastatic disease that is refractory to chemotherapy and remains confined to the uterus (34, 41).

The overall cure rate for patients with nonmetastatic disease is nearly 100% (1, 33, 34, 37, 42). When chemotherapy is given for an additional 1–2 cycles after the first normal hCG value, recurrence rates are less than 5% (39).

▶ *How is low-risk metastatic gestational trophoblastic disease treated?*

Patients with metastatic gestational trophoblastic disease who lack any of the clinical high-risk factors (33–35) or have a FIGO risk score less than 7 (14) 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 (33, 42, 43). Approximately 40% of these patients will require alternative therapy to achieve remission (43); however, essentially all patients with low-risk metastatic gestational trophoblastic disease can be cured with conventional chemotherapy (31, 33, 34, 42). Hysterectomy in conjunction with chemotherapy also may decrease the amount of chemotherapy required to achieve remission in these patients (34). 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 (39).

▶ *How is high-risk metastatic gestational trophoblastic disease treated?*

Patients with 1 or more of the Clinical Classification system risk factors (33–35) or a FIGO risk score of 7 or higher (14) have high-risk disease. They will require multiagent chemotherapy with additional surgery or radiation often incorporated into treatment (34). Survival rates reported by trophoblastic disease centers have been reported as high as 84% (31–34, 36, 44). In contrast to 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 (34).

Aggressive treatment with multiagent chemotherapy is an important component for management of these patients. Triple therapy with methotrexate, dactinomycin, and either chlorambucil or cyclophosphamide was the standard regimen for many years in the United States (4, 35, 44). In a randomized trial, a more complex multiagent regimen was not proved to be superior to triple therapy with methotrexate, dactinomycin, and either chlorambucil or cyclophosphamide (44, 45). More recent regimens have incorporated etoposide with or without cisplatin into combination chemotherapy (4, 36, 46–48) with high rates of success but with an increased risk for leukemia in survivors. A randomized comparison of the newer combinations with triple therapy with methotrexate, dactinomycin, and either chlorambucil or cyclophosphamide would provide helpful information.

Management of cerebral metastases is controversial. Radiation therapy has been used concurrently with chemotherapy in an attempt to limit acute hemorrhagic complications from these metastases. Brain irradiation combined with systemic chemotherapy is successful in controlling brain metastases with cure rates up to 75% in patients with brain metastases (49). However, a similar primary remission rate also has been reported among patients treated with combination regimens that incorporated high-dose systemic methotrexate combined with intrathecal methotrexate infusions without brain irradiation (46). The best treatment for liver or other high-risk sites of metastases has not been established. Even with intense chemotherapy, additional surgery may be necessary to control hemorrhage from metastases, remove chemoresistant disease, or treat other complications to stabilize high-risk patients during therapy (34, 41).

Chemotherapy is continued until hCG values have normalized, followed by at least 2 or 3 courses of maintenance chemotherapy in the hope 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 (39).

▶ *What is the recommended surveillance following completion of chemotherapy for malignant gestational trophoblastic disease?*

After hCG remission has been achieved, patients with malignant gestational trophoblastic disease should

undergo serial determinations of hCG levels at 2-week intervals for the first 3 months of remission and then at 1-month intervals until monitoring has shown 1 year of normal hCG levels. The risk of recurrence after 1 year of remission is less than 1% (39), but late recurrences have been observed rarely.

Patients should be counseled to use a reliable form of hormonal contraception during the first year of remission. Because of the 1–2% risk for a second mole in subsequent pregnancies (20), early ultrasound examination is recommended for all future pregnancies. There does not appear to be an increase in the risk of congenital malformations or other complications related to pregnancy (20).

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- In women of reproductive age with abnormal bleeding or symptoms that could be caused by a malignancy, β-hCG levels should be evaluated to facilitate early diagnosis and treatment of gestational trophoblastic disease.
- In patients with molar pregnancy, the preferred method of evacuation is suction D&C. After molar evacuation, all patients should be monitored with serial hCG determinations to diagnose and treat malignant sequelae promptly.
- Oral contraceptives have been demonstrated to be safe and effective during posttreatment monitoring based on randomized controlled trials.
- Women with nonmetastatic gestational trophoblastic disease should be treated with single-agent chemotherapy.
- For women with nonmetastatic gestational trophoblastic disease, weekly doses of 30–50 mg/m^2 of intramuscular methotrexate has been found to be the most cost-effective treatment when taking efficacy, toxicity, and cost into consideration.
- Women with metastatic gestational trophoblastic disease should be referred to specialists with experience treating this disease.
- Women with high-risk metastatic disease should be treated with multiagent chemotherapy. This includes triple therapy with methotrexate, dactinomycin, and either chlorambucil or cyclophosphamide. More recent regimens further incorporate etoposide with or without cisplatin into combination chemotherapy.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- 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.
- Serial quantitative serum hCG determinations should be performed using a commercially available assay capable of detecting β-hCG to baseline values (<5 mIU/mL). Ideally, serum hCG levels should be obtained within 48 hours of evacuation, every 1–2 weeks while elevated, and then at 1–2 month intervals for an additional 6–12 months.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Abnormal bleeding for more than 6 weeks following any pregnancy should be evaluated with hCG testing to exclude a new pregnancy or gestational trophoblastic disease.
- In compliant patients, the low morbidity and mortality achieved by monitoring patients with serial hCG determinations and instituting chemotherapy only in patients with postmolar gestational trophoblastic disease outweighs the potential risk and small benefit of routine prophylactic chemotherapy after evacuation of a molar pregnancy.
- Serious complications are not uncommon in women with a uterus size greater than a 16-week gestation, so they should be managed by physicians experienced in the prevention and management of complications.
- Patients for whom initial therapy for nonmetastatic or low-risk metastatic disease fails and those with high-risk malignant gestational trophoblastic disease should be managed in consultation with individuals or facilities with expertise in the complex, multimodality treatment of these patients.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and February 2004. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least 1 properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than 1 center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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