Practice Guidelines: Gestational Trophoblastic Disease

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Gestational trophoblastic disease is a term applied to a rare group of tumors that have several common characteristics: the tumor cells arise in the fetal chorion during pregnancy; the vast majority of the tumors make human chorionic gonadotropin (hCG); the amount of hCG produced is proportional to the amount of viable tumor; and they are sensitive to a variety of cytotoxic chemotherapeutic agents. Histopathologic diagnoses included in this group of tumors are:

- Hydatidiform mole, complete or partial
- Gestational choriocarcinoma
- Placental site trophoblastic tumor

Although they have these common characteristics, they differ in other characteristics: histopathology, type of pregnancy in which the tumor arises, clinical course if untreated with chemotherapy, and likelihood of responding to treatment. Since this group of tumors varies greatly in malignant potential, it is critical that the clinician know enough about the various clinical patterns so that a patient with an essentially benign condition is not overtreated and a patient with a potentially fatal condition can be treated as early and as aggressively as possible.

Screening

Although all of these tumors arise in pregnancy, it is only possible in molar pregnancies to know or suspect the type of trophoblastic tumor while the pregnancy is ongoing. Complete hydatidiform moles have characteristics that make them likely to be diagnosed before the uterus is evacuated: the villi are diffusely involved and often quite large (hydropic, "grape-like"); trophoblastic overgrowth is common; uterine size is often in excess of expected size based on dates; theca lutein cysts are common; hCG levels are often greater than expected for corresponding dates of normal pregnancies; and there is no evidence of fetal parts.

With the common practice of routine ultrasonography in the first trimester of pregnancy and the characteristic appearance of the prominent villi on ultrasonographic examination, it is common for complete hydatidiform moles to be diagnosed before there is vaginal spotting or passage of grossly detectable vesicles. The likelihood of there being a need for subsequent chemotherapy after evacuation of the uterus varies from 10% to 25% and depends largely on the criteria the clinician follows to define this need.

Partial hydatidiform moles are much less likely to be diagnosed while still in utero. Much less placenta is involved in hydropic villous change; trophoblastic proliferation is focal and slight; fetal remnants may be seen; the uterus tends to be small; theca lutein cysts are rare; and the hCG level is not excessive. The sonographic findings often fail to result in the correct diagnosis. Although the likelihood of so-called "malignant sequelae" (molar proliferation or transition to choriocarcinoma) is less than that associated with a complete hydatidiform mole, the fact that these have been reported requires that all patients with molar pregnancies undergo the same surveillance. This use of hCG assays will be discussed below.

Gestational choriocarcinoma is the highly malignant form of gestational trophoblastic disease that, unfortunately, can arise in any form of pregnancy. It can follow an apparently normal pregnancy, any type of abortion (spontaneous, ectopic, or elective), and can develop from malignant transition in a molar pregnancy. Because of the rarity of it developing after a term delivery (1/12,000 to 1/40,000), it is not practical to follow patients after term deliveries or even miscarriages with hCG assays to
detect malignant disease. Placental site trophoblastic tumors are the rarest form of gestational trophoblastic disease and were belatedly recognized as a separate histopathologic and clinical entity. They are composed of only one cell type, intermediate trophoblast, and, like gestational choriocarcinoma, they can follow any type of pregnancy. Their clinical course is unpredictable, for they may be cured by a dilation and curettage (D&C) or persist and metastasize. Unfortunately, they respond poorly to chemotherapy and produce hCG unreliably. Early surgery, including hysterectomy, is important. Their rarity is fortunate for we have little control over their clinical outcome if surgery is not successful.

**Diagnosis**

Although the diagnosis of a molar pregnancy identifies a patient who needs follow-up hCG assays to identify those needing further therapy, the early diagnosis of malignant trophoblastic disease following a term pregnancy or abortion often requires suspicion for the diagnosis when a woman of reproductive age presents with an undiagnosed tumor or bleeding from a metastatic site. Some patients will be fortunate enough to have persistent tumor limited to the uterus and have their diagnosis established by D&C, but most will present with metastatic disease. Sites of metastases, in descending order, are lung, vagina, brain, liver, gastrointestinal tract, and kidney. Because the time interval from the antecedent normal pregnancy to the onset of symptoms of metastatic disease can vary from months (usual) to years (rare), clinicians must be aware of the possibility that a malignant trophoblastic tumor may be the cause of abnormal bleeding or an unexplained tumor in virtually any organ. One sensitive hCG assay will determine if the woman has a rare, but highly curable, gestational choriocarcinoma.

Diagnostic procedures that are needed to properly classify patients begin with a chest x-ray to detect pulmonary metastases. If there is no abnormal bleeding or worrisome symptoms from other organs and the chest x-ray is clear, an argument can be made for classifying the patient as having a nonmetastatic tumor. Even though a CT scan might reveal disease detectable by regular x-rays, 40% of patients with suspected malignant gestational trophoblastic disease and a clear chest x-ray will have small metastases detected by CT scans of the lungs.

If pulmonary metastases are detected, CT scans of the brain, abdomen, and pelvis are indicated. In the presence of questionable liver changes on CT scan, a sonogram may be more useful. Similarly, an MRI or serum/cerebrospinal fluid (CSF) ratio of beta hCG may be more sensitive in detecting brain metastases. If there is gastrointestinal (GI) bleeding, upper and lower GI tract endoscopy is indicated. If GI bleeding is heavy, an arteriogram to detect bleeding sites is useful prior to surgery. Hematuria calls for an intravenous pyelogram and cystoscopy.

All of these tests may contribute to the localization of disease and the assignment of proper stage or World Health Organization (WHO) score, but they are not as useful in following response to chemotherapy, as is the weekly assay of hCG levels. A reliable assay of hCG is critical for diagnosis, monitoring of response to therapy, defining complete response, and surveillance for recurrence. None of the x-rays or scans is as reliable for these purposes.

**Staging (Classification of Disease)**

Unlike all other staging systems for gynecologic malignancies, the two most often used systems for categorizing patients with gestational trophoblastic disease are based on more than histology and location of the disease. There are several reasons for this. The most important reason is that the two most commonly used staging classifications, the National Institutes of Health (NIH) clinical classification (Table 1) and the Bagshawe/WHO system (Table 2) are actually designed to allow the proper selection of chemotherapy rather than to plan surgery or radiation therapy. Also, there is little emphasis on the histology of metastatic lesions (metastatic molar tissue or choriocarcinoma) because their treatment is the same. Finally, these two classifications take into consideration dynamic factors in the clinical course of the patient (level of hCG, time since onset of disease, prior chemotherapy, and number as well as site of metastases). Because of this, they define the risk of a patient not responding to chemotherapy at any given time when new treatment is being started. Because there is such a wide range of effective chemotherapeutic agents that can be used alone or in various combinations in patients with gestational trophoblastic disease, the purpose of these two systems is to allow the clinician to select treatment that is effective in a risk category but no more toxic or dangerous than is necessary. In the low-risk categories, new developments have as their goal the avoidance of toxicity, decrease of costs, or similar considerations, without a decrease in cure rates. In the high-risk category, the goal is to increase the cure rate.

**Treatment**
Because chemotherapy is effective in treating both metastatic and nonmetastatic disease, and surgery can still be curative in disease limited to the uterus, one of the important considerations in choosing treatment is the patient’s desire to preserve her childbearing potential. This is more important in patients with nonmetastatic disease than in those with metastases. In considering treatment of patients with nonmetastatic disease, the histologic pattern of the uterine disease is important.

**Nonmetastatic Disease**

**Unevacuated Hydatidiform Mole** If a patient has passed molar vesicles or has had a sonogram that is diagnostic of a hydatidiform mole, treatment begins with evacuation of the uterine contents. The consensus now is that the less invasive or active the process, the less likely there is to be molar persistence or spread. A suction curettage followed by oxytocin infusion and a gentle curettage is preferred. In an older woman with no desire for more children, a hysterectomy may be considered.

**Postevacuation Hydatidiform Mole** Careful follow-up and evaluation of patients who have undergone evacuation of a molar pregnancy are critical to identifying those at risk of developing serious complications due to tumor. At the onset, they need a chest x-ray and repeated assays of their serum beta-hCG levels every 1 to 2 weeks. In addition, they need regular pelvic examinations to evaluate uterine involution, condition of the ovaries, and the presence of uterine bleeding. If bleeding starts after a period of cessation, great care must be taken during the next examination because of the possibility of there being vaginal metastases that can bleed disastrously.

The most useful measure of tumor activity is the pattern of beta-hCG levels. If beta-hCG values decrease progressively and reach a level of normal in that assay, there is little chance of persistence of molar tissue or transition to choriocarcinoma. If, however, the level plateaus (similar level for 2 to 3 consecutive weeks) or rises, chemotherapy is indicated. Although this group may be considered to have developed malignant sequelae, this is based on the future risk of their developing local complications or metastases, rather than an actual change in the histology of the lesion. The vast majority will be cured with a relatively nontoxic, single-agent regimen and retain reproductive function, although as many as 10% may require a hysterectomy.

**Nonmetastatic Choriocarcinoma** After an abortion or term delivery, a small number of patients will have vaginal bleeding, which leads to a D&C showing choriocarcinoma. Although beta-hCG levels are useful for determining response to therapy, treatment should begin at once, regardless of their level and without waiting to see if they decrease. If x-rays and scans show no evidence of metastatic disease, the decision concerning hysterectomy will be based on the patient’s desire for further childbearing. If hysterectomy is carried out, most gestational trophoblastic disease centers would do it during a course of chemotherapy, because surgery alone in this situation cures only approximately 40%. If only chemotherapy is used, it can be single-agent therapy, but a shift to combination chemotherapy should occur early if there is a suspicion of the development of drug resistance.

**Nonmetastatic Placental Site Trophoblastic Tumor** This rare condition can be found at the time of D&C for vaginal bleeding after any type of pregnancy. Although there are reports of cures after only a D&C, their lack of response to chemotherapy and their inconsistent production of hCG causes great concern. If there is evidence of persistent tumor and no evidence of metastatic disease, hysterectomy should be an early choice.

**Metastatic Disease**

Patients in the childbearing age range who have evidence of progressive metastatic disease, an elevated level of hCG, and a history of a relatively recent pregnancy event should be evaluated to determine their risk category in either the NIH or the WHO classification system. If there is a history of a molar pregnancy or a tissue diagnosis of choriocarcinoma based on a D&C or hysterectomy specimen, the diagnosis of a gestational trophoblastic disease entity is well established. However, without these, the question of whether to seek a histologic confirmation is raised. There are many types of tumors that ectopically produce hCG and this raises the question of diagnosis. However, most do not reach the high levels of hCG associated with metastatic gestational trophoblastic disease. When the diagnosis is not certain, an argument can be made for giving the first course of chemotherapy as a therapeutic test, rather than run the risk of trying to biopsy the highly vascular trophoblastic malignancy.

Once the diagnosis has been assumed or established, the evaluation focuses on determining the location and extent of disease, as well as the hCG level. The purpose is to define a risk category on the basis of which chemotherapy regimen can be chosen. The goal is to treat low-risk patients with the least toxic or expensive regimens to which there is known response, while monitoring hCG levels to define resistance early. If resistance develops, the patients are, in essence, reclassified and treated with more toxic combination therapy. Medium-risk patients are begun on either single-agent
therapy or combination chemotherapy, and high-risk patients are given maximal therapy, often including radiation therapy, adjunctive surgery, and nutritional and bone marrow support in addition to multidrug combination therapy.

**Low-Risk Patients (WHO Score, 4 or Less)** These patients can be initially treated with any one of several therapeutic regimens that utilize single agents. Complete responses have been reported in essentially all patients. In the past, patients whose disease was not cleared with one agent were shifted to another single agent. Currently, the consensus is that it is safer to shift to combination therapy, such as MAC (methotrexate, actinomycin D, and cyclophosphamide/chlorambucil). Once it is clear that single-agent therapy is not succeeding, the shift to more aggressive treatment is important to prevent the development of drug resistance.

**Medium-Risk Patients (WHO Score, 5 to 7)** These patients should be started on a regimen that includes a combination of drugs. MAC-based combinations are most commonly used. If a complete response is not reached on this regimen, most investigators shift to the combination EMA-CO (etoposide, methotrexate, actinomycin D, alternating with cyclophosphamide and Oncovin), which was initially used at Charing Cross and has become the most commonly used regimen for high-risk patients. When medium-risk patients are not cured by combination therapy, their WHO score increases by 4 and they are reclassified into the high-risk category. The therapeutic goal in this group should be the cure of essentially all patients, which has been reported from several institutions.

**High-Risk Patients (WHO Score, 8 or Greater)** This group of patients presents the greatest challenge to successful chemotherapy. Because it includes patients with metastases to the brain, liver, and GI tract, these patients can succumb early in treatment due to massive bleeding, and they are also more likely to develop drug resistance after prolonged chemotherapy. The most successful reported combination is EMA-CO. Newlands and colleagues at Charing Cross have reported a 80% complete remission rate in patients in this risk category. To achieve this, they have also utilized salvage chemotherapy and surgery to remove resistant foci of tumor.

When EMA-CO does not clear the disease, several other drugs and drug combinations have shown responses and are useful as salvage therapy. Despite these new developments, this risk category accounts for virtually all of the deaths of gestational trophoblastic disease patients who receive therapy in specialized treatment centers. Patients in all of the above treatment categories should be followed with regular beta-hCG assays, as they are the most sensitive indicators of tumor activity. They should be done weekly during treatment and every 2 weeks for 2 to 3 months thereafter, followed by monthly assays up to 6 months and every 2 months thereafter.

Follow-up studies after 1 year should be limited to patients who have been treated for metastatic disease, and these tests should be done yearly. Patients who were followed after evacuation of a molar pregnancy and never required chemotherapy can be taken off regular surveillance after 1 year unless they have a subsequent pregnancy. If they do, a sonogram should be done at 8 to 12 weeks to confirm the presence of a normal gestational sac. One beta-hCG assay should be done 4 to 6 weeks after delivery to rule out the rare, but reported, reactivation of a previous trophoblastic tumor.

**Special Considerations**
Several referral areas of interest related to the treatment and follow-up of patients with gestational trophoblastic disease deserve brief discussion.

**Referral to Specialized Gestational Trophoblastic Disease Treatment Centers**
A common question is which patients should be referred to centers that have developed special interests and skills in the study and treatment of women with gestational trophoblastic disease. Because most deaths of patients with gestational trophoblastic disease occur either from the progression of advanced disease before any treatment is given or the development of drug resistance when inadequate treatment is given, a simple answer to the question is that a patient should be referred when she is in a high-risk category. Only a small percentage of gestational trophoblastic disease patients need such a referral. However, those who do need it can benefit from the center’s experience with managing drug toxicity and utilizing marrow and nutritional support when needed. These centers also have access to new investigational drugs, some of which are promising.

**Role of Surgery**
Although the primary areas of emphasis in treating gestational trophoblastic disease are chemotherapy and the use of hCG assays to monitor response to this treatment, surgery still plays an important part in the treatment of some patients. The evacuation of a molar pregnancy is a potentially complicated procedure and must be done carefully. In patients with no evidence of
disease outside the uterus and no desire to preserve the childbearing potential, hysterectomy is often preferable to prolonged chemotherapy in patients with either choriocarcinoma or persistent molar disease. Based on historical controls, this is more successful if carried out during a course of single-agent chemotherapy.

Even in the presence of metastatic disease, removal of a uterus with trophoblastic tissue has been shown to decrease the number of courses of chemotherapy needed to achieve remission. In the Duke series, this procedure was beneficial in low- or medium-risk patients but not in high-risk patients. There are two other indications for surgery in patients with metastatic disease: treatment of complications and removal of the only residual site of disease following partial response to chemotherapy.

**Long-Term Follow-Up of Patients Treated With Chemotherapy**

Although there are sporadic reports of recurrent disease after long periods of quiescence, the primary areas of interest are the outcome of subsequent pregnancies and the long-term effects of chemotherapy. In an era when attention is being paid to the quality of life of cancer survivors, it is reassuring to report the successful preservation of childbearing potential in most women treated for gestational trophoblastic disease. More importantly, with the exception of the increased rate of molar pregnancy in patients with a previous mole, recorded series show no increase in fetal or pregnancy complications. Women successfully treated with chemotherapy for gestational trophoblastic disease rarely develop treatment-related second malignancies.

**Treatment of Recurrence**

The likelihood of gestational trophoblastic disease recurring after completion of chemotherapy is related to initial risk status. Patients with high WHO scores (high-risk patients) are more likely to have recurrence than those with low-risk disease. Chemotherapy is used again. Its selection is based on previous response of the tumor.

**References:**


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