**Gestational Trophoblastic Neoplasia**

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**Learning Objectives:** After participating in this CME activity, the obstetrician/gynecologist should be better able to:
1. Apply diagnostic criteria to identify invasive gestational trophoblastic neoplasia.
2. Describe staging and risk stratification to guide management of gestational trophoblastic neoplasia.
3. Explain characteristics and management principles of placental site trophoblastic tumor and epithelioid trophoblastic tumor.

**Key Words:** Gestational trophoblastic neoplasia, Trophoblastic tumor

Gestational trophoblastic neoplasia (GTN) is the collective term used to describe the malignant transformation of placental villous and extravillous trophoblasts, arising from either a normal or an abnormal pregnancy. GTN includes invasive moles, choriocarcinoma, placental site trophoblastic tumors, and epithelioid trophoblastic tumors. The most common GTN is the invasive mole, which occurs in 15% to 30% of patients with a complete hydatidiform mole and 2% of patients with a partial mole. Although the prevalence of hydatidiform mole is 1 in 1200 pregnancies, the prevalence of gestational choriocarcinoma is 1 in 40,000 pregnancies or approximately 1 in 40 complete moles. Choriocarcinoma may also occur spontaneously, after a term pregnancy. The prevalence of choriocarcinoma after a normal term pregnancy is 1 in 160,000 pregnancies.¹

With prompt diagnosis and appropriate therapy in patients with GTN, the prognosis is excellent. The goal of this article is to update the practicing obstetrician/gynecologist about the diagnosis, management, and counseling of patients with GTN.

**Diagnosis**

Most patients with GTN are diagnosed by a plateau or increase in serum human chorionic gonadotropin (hCG) levels after evacuation of a hydatidiform mole. International Federation of Gynecology and Obstetrics (FIGO) guidelines for diagnosis are as follows: 4 or more hCG measurements demonstrating a plateau over 3 weeks; an increase in hCG levels of 10% or more in 3 or more measurements over 2 weeks; histologic diagnosis of choriocarcinoma; or detectable hCG levels 6 months after evacuation of a molar pregnancy.² Interval pregnancy must be excluded. To minimize the risk of a confounding pregnancy, it is vital that patients use contraception after treatment of molar pregnancy until hCG levels reach an undetectable level. Risk of malignancy is increased in molar pregnancies in which the starting hCG value is higher than 100,000 mIU/mL, uterine size is larger than appropriate for gestational age, and theca lutein ovarian cysts larger than 6 cm in diameter are present.³

Upon identification of GTN, the patient must be evaluated for metastases. Metastases in the lung are most common, followed by lower genital tract, brain, and liver. Metastases should not be biopsied, as lesions are often highly vascular. Lung metastases are often asymptomatic, but patients may present with hemoptysis, shortness of breath, or chest pain. Lower genital tract metastases appear as purple or blue-black papules or nodules, and often they are accompanied by symptoms of bloody or purulent discharge. Lower genital tract metastases are especially
vascular and may result in severe hemorrhage if biopsied.4

Brain and liver metastases are unlikely to be found in patients without metastases to either the lungs or vagina. Patients with brain metastases often present with vomiting, seizures, headache, slurred speech, hemiparesis, or visual disturbance resulting from increased intracranial pressure or intracerebral bleeding. Patients with liver involvement most commonly present with symptoms related to other metastases (pulmonary, brain, or lower genital tract) rather than with hepatic symptomatology, although abdominal tenderness or jaundice may be present. Peritoneal signs may be present in the setting of hemoperitoneum due to bleeding from an abdominal metastasis.5

Given the high propensity for metastatic disease, a thorough evaluation is important, even if the patient does not exhibit symptoms of metastasis. In addition to serial hCG measurements to assess response to therapy, appropriate laboratory studies include a complete blood count and liver function testing to assess for anemia and evaluate for liver metastases, respectively.1 Chest radiography is recommended to assess for pulmonary metastases. CT of the chest is optional. Micrometastases are detected using CT in 40% to 45% of patients with a negative chest radiograph; however, the clinical significance of this finding has not been demonstrated. Furthermore, lung metastases seen only on CT of the chest cannot be used in staging.6 CT of the abdomen and pelvis is recommended to assess for abdominal metastases, as is MRI of the head to assess for brain metastases. Pelvic ultrasound may reveal residual tumor in the uterus.2

FIGO classification for staging of GTN is shown in Table 1. Staging includes use of the World Health Organization (WHO) prognostic score as adapted by FIGO (Table 2).7

Of the 2 numbers (stage and score), the WHO score is more useful for prognosis and treatment guidance. A patient with a score lower than 7 is considered to have low-risk disease, whereas a score of 7 or higher is considered high-risk disease. Patients with low-risk disease have a nearly 100% probability of cure with chemotherapy. With high-risk disease, the cure rate is approximately 75%.1

**Morphology**

**Invasive Mole**

An invasive mole arises from a complete or partial molar pregnancy. They are characterized by growth of molar villi and tropheoblast into uterine myometrium with hemorrhage and necrosis. Histologically, they appear similar to a noninvasive hydatidiform mole, except for their destructive growth. The tumor may invade all the way to the serosa and cause intra-abdominal hemorrhage.7 Given that a hysterectomy is seldom performed in patients with this pathologic entity, these tumors most often are diagnosed clinically by the trend in hCG levels. Patients with a histologic diagnosis of hydatidiform mole who are determined to have metastases (most commonly in the lungs) are classified as having an invasive mole.

**Choriocarcinoma**

A hydatidiform mole precedes half of choriocarcinomas. One quarter of choriocarcinomas follow an abortion, 22% follow a term pregnancy, and 3% arise after an ectopic pregnancy. Choriocarcinomas lack chorionic villi, but they contain sheets of...
trophoblasts and hemorrhage with necrosis. They frequently spread hematogenously, most often to the lung, brain, or liver. Choriocarcinomas also may arise without any antecedent pregnancy in the ovary as a germ cell tumor, although this is much less common than gestational choriocarcinoma.

Placental Site Trophoblastic Tumor and Epithelioid Trophoblastic Tumor

Placental site trophoblastic tumor (PSTT) is a rare malignancy occurring in 1 of 100,000 pregnancies. It first was described in the literature in 1976. Unlike invasive hydatidiform mole or choriocarcinoma, the mortality rate is reported to range from 6.5% to 20%. Although PSTT can occur after any type of pregnancy, the most common antecedent pregnancy is a full-term pregnancy. PSTT is characterized histologically by a monomorphic population of placental implantation site-like intermediate trophoblasts rather than the dimorphic population (cytotrophoblasts and syncytiotrophoblasts) typical of choriocarcinomas. The intermediate trophoblasts are large polyhedral cells with irregular hyperchromatic nuclei. These cells are typically found infiltrating the myometrium as single cells or sheets of cells. Unlike other GTN, PSTT secretes more human placental lactogen (hPL) than hCG, which may lead to a delay in diagnosis. Suspicion for PSTT should be high if sonographic or MRI findings reveal an infiltrating myometrial lesion with persistently low levels of hCG. Sensitivity to chemotherapy is low with PSTT compared with other kinds of GTN. Treatment strategy is discussed below.

First described in 1998, epithelioid trophoblastic tumor (ETT) is a chorionic-type intermediate trophoblast. Histologically, ETT is characterized by nodular growth of nested and/or cored monomorphic epithelioid cells. ETT frequently involves the lower uterine segment and endocervix, potentially confounding its diagnosis further. Given its epithelioid appearance, it can be misdiagnosed as a squamous cell carcinoma. It also could mimic a high-grade squamous intraepithelial lesion when it replaces the endocervical glandular epithelium. Similar to squamous lesions, the cells of ETT are positive for cytokeratin and p63 immunostaining. Focal immunostaining for hCG and hPL may be present. Like PSTT, ETT most often follows a normal term pregnancy.

Both PSTT and ETT may present months to years after the antecedent pregnancy. Growth is slow, and the tumors often remain stage I for an extended period. However, nonspecific symptoms such as abnormal vaginal bleeding or amenorrhea make diagnosis difficult at an early stage, and many women are diagnosed with later-stage disease. ETT may secrete hCG, but often in amounts below 1000 IU/L, making serum hCG a somewhat unreliable tumor marker. Nonetheless, hCG levels in excess of 100,000 IU/L have been reported in PSTT and ETT. hPL is not associated with ETT.

**Treatment**

**Medical Therapy**

Treatment for GTN is guided by modified WHO score (Table 2). Low-risk disease is defined as a score less than 7. Treatment comprises single-agent chemotherapy with either methotrexate or actinomycin D; various treatment regimens are available. Gynecologic Oncology Group (GOG) trial 0174 investigated these 2 drugs and demonstrated better first-line response rate for biweekly pulsed intravenously administered actinomycin D 1.25 mg/m² compared with weekly intramuscular methotrexate 30 mg/m² (70% vs 53%, \(P = 0.01\)). However, it has been suggested that if a weekly methotrexate dose of 50 mg/m² had been used in the trial, the response rate would have been comparable to that of the actinomycin D regimen. No matter which of these agents is used first, low-risk GTN is highly curable. More common

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**Table 1. Staging of Gestational Trophoblastic Neoplasia**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disease confined to uterus</td>
</tr>
<tr>
<td>II</td>
<td>GTN extends outside the uterus but is limited to genital structures (adnexa, vagina, and broad ligament)</td>
</tr>
<tr>
<td>III</td>
<td>GTN extends to the lungs, with or without genital tract involvement</td>
</tr>
<tr>
<td>IV</td>
<td>All other metastatic sites</td>
</tr>
</tbody>
</table>

GTN, gestational trophoblastic neoplasia.

**Table 2. Modified World Health Organization Scoring of Gestational Trophoblastic Neoplasia**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>&lt;40</td>
<td>≥40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval months from index pregnancy</td>
<td>&lt;4</td>
<td>4–7</td>
<td>7–13</td>
<td>&gt;13</td>
</tr>
<tr>
<td>Pretreatment serum hCG level</td>
<td>&lt;1000</td>
<td>&lt;10,000</td>
<td>&lt;100,000</td>
<td>≥100,000</td>
</tr>
<tr>
<td>Largest tumor size</td>
<td>3–5 cm</td>
<td>≥5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen/kidney</td>
<td>Gastrointestinal</td>
<td>Liver/brain</td>
</tr>
<tr>
<td>Number of metastases</td>
<td>1–4</td>
<td>5–8</td>
<td>&gt;8</td>
<td></td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>Single drug</td>
<td></td>
<td>Two or more drugs</td>
<td></td>
</tr>
</tbody>
</table>

*Total score determined by adding scores for all factors.

hCG, human chorionic gonadotropin.
methotrexate regimens include 5- and 8-day intramuscular regimens, with cure rates of approximately 70% to 80%. The 5-day regimen consists of 0.4 mg/kg (not to exceed 30 mg) of intramuscular or intravenous methotrexate administered daily for 5 days. This is repeated every 14 to 16 days. The 8-day regimen involves 1 mg/kg of methotrexate given on days 1, 3, 5, and 7, with folinic acid rescue on days 2, 4, 6, and 8. This is repeated every 14 to 16 days. HCG levels should be drawn weekly during the course of therapy.12,13

Treatment should be continued until hCG level has normalized and then continued for an additional 6 weeks. If hCG levels plateau or increase, a switch to the alternate drug should be made. Upward of 90% of patients will achieve cure with single-agent therapy. Should metastatic disease develop during treatment or if both single-agent regimens fail, multiagent chemotherapy is needed.14

A WHO score of 7 or above is associated with increased risk for chemotherapy failure when a single agent is used. Multiagent chemotherapy regimens are used as first-line therapy in these patients. Since the 1980s, the preferred regimen has been a combination of etoposide, high-dose methotrexate with folinic acid rescue, and actinomycin D administered in the first week of a 2-week cycle; and cyclophosphamide and vincristine on the second week (EMA-CO).3 Response rates of approximately 75% have been reported, with long-term survival rates of 85% to 94%. The regimen is relatively well tolerated, with the main toxicity being myelosuppression. In one study, neutropenia requiring a delay in therapy was seen in 14% of patients. Anemia requiring blood transfusion occurred in 5.8% of patients, and severe neutropenia occurred in only 1.9% of patients. If EMA-CO fails, patients may undergo multiagent therapy with EMA-EP. In this regimen, etoposide and cisplatin are given on day 8 of the cycle instead of cyclophosphamide and vincristine. Like single-agent therapy, this regimen should be continued for 6 weeks (ie, 3 cycles) after hCG levels return to normal.14

Patients with central nervous system metastases should undergo whole brain irradiation (versus surgical excision or stereotactic irradiation) at initiation of chemotherapy.15 EMA-CO therapy is used, but the methotrexate dose is increased to attain therapeutic levels in cerebrospinal fluid.14 During brain irradiation, dexamethasone is administered to reduce brain edema.1 Survival rates in these patients have been reported to range from 50% to 80%.

Salvage chemotherapy in resistant or recurrent disease usually consists first of EMA-EP therapy. Other regimens reported include vinblastine, bleomycin, and cisplatin (VBP); and 5-fluorouracil and floxuridine. High-dose chemotherapy with stem cell rescue also is an option in patients with multidrug-resistant disease.7

After chemotherapy, many women retain normal ovarian function without a noted increase in congenital anomalies; however, increased stillbirth rates have been noted.16 Because of the need for close follow-up of hCG levels after therapy, it is important to delay pregnancy for at least 1 year after serum hCG normalization. Late recurrences occur in less than 2% of patients.

**Surgical Therapy**

Initial management with hysterectomy has been demonstrated to decrease the number of chemotherapy cycles needed to achieve remission.17 Similarly, repeat dilation and curettage for residual tissue in the uterine cavity has been investigated. A study by the GOG demonstrated a 40% remission rate in patients with low-risk GTN who underwent repeat dilation and curettage, avoiding chemotherapy.18 Debulking of lung nodules and removal of brain metastases may improve response to chemotherapy. Wedge resection of solitary myometrial lesions may be similarly beneficial, especially in patients with chemotherapy-resistant disease.19

In addition to tumor debulking, surgical therapy is often used to control bleeding. Uterine or hypogastric artery ligation or embolization may be employed in patients with uncontrolled bleeding. In some patients, hysterectomy may be necessary to control bleeding. In patients with cerebral hemorrhage from metastatic disease, craniotomy may be required to control bleeding and provide decompression.15

**Placental Site Trophoblastic Tumor and Epithelioid Trophoblastic Tumor**

Although rare, PSTT and ETT are more chemoresistant and thus require more aggressive intervention. WHO scoring is less useful with these tumors than in patients with other types of GTN. Factors associated with a poor prognosis include metastatic disease; long interval (>4 years) from antecedent pregnancy; deep myometrial invasion; tumor necrosis; and mitotic count higher than 6/10 per high-powered field.14 Multiple studies have demonstrated time from antecedent pregnancy to be the most important risk factor, with survival rates dramatically worsening as the time interval increases.9 Hysterectomy is recommended as the first step in management. In the absence of metastases, the ovaries may be retained. The role of retroperitoneal node dissection has not been determined. In one study that included patients with newly diagnosed disease and with recurrent disease, lymph node involvement was documented in 6% of cases.20 Some authors advocate lymph node dissection in patients with presumed stage I disease with deep myometrial invasion or with bulky lymph nodes.9 Patients with poor prognostic factors and those with metastatic disease should receive adjuvant chemotherapy. EMA-EP is the most common regimen. Overall survival of patients with metastatic disease treated with EMA-EP is 50%,10,14,21

Monitoring of treatment effectiveness has proven to be difficult, as neither tumor reliably secretes hCG. PSTT secretes hPL, but hPL has not been established as a tumor marker for monitoring treatment response. Most often, at least 4 cycles of EMA-EP are used and hCG levels monitored. Resection of residual or recurrent tumor after chemotherapy has been suggested, even if the serum hCG level has normalized.9,22

Salvage regimens have not been well studied. Gemcitabine has been used; as has bleomycin, etoposide, and cisplatin
(BEP); and high-dose chemotherapy with stem cell rescue. PSTT has been demonstrated to stain for vascular endothelial growth factor and epidermal growth factor receptor. Therefore, the use of biologic agents such as bevacizumab, erlotinib, or sunitinib could be considered.9,10

Conclusion

GTN is a highly curable malignancy. With close surveillance after evacuation of a complete or partial hydatidiform mole, GTN can be detected early, and low-risk disease may be treated with single-agent chemotherapy. If residual tumor in the uterine cavity is detected by ultrasound, repeat dilation and curettage or hysterectomy may obviate the need for chemotherapy or may decrease the total amount of chemotherapy needed to achieve a cure. Even in the event of single-agent therapy failure, remission rates are high with use of combination regimens such as EMA-CO.

At diagnosis of GTN, all patients should be evaluated thoroughly for metastatic disease before treatment begins. Patients with high-risk disease should be treated with combination therapy such as EMA-CO or EMA-EP. Long-term survival is good in patients with high-risk disease who are treated aggressively.

PSTT and ETT are rare types of GTN that are resistant to chemotherapy. Because of low serum hCG levels, they are difficult to diagnose. The most significant factor for poor prognosis in patients without evidence of metastasis is an extended interval after the antecedent pregnancy. Surgical resection is recommended. Combination chemotherapy (EMA-EP) is administered to patients with metastatic disease or high-risk factors.

REFERENCES

1. GTN diagnostic criteria include all of the following except
   A. pathologic diagnosis of choriocarcinoma
   B. plateau of hCG levels for 4 measurements over 3 weeks
   C. pathologic diagnosis of molar pregnancy
   D. increase in hCG levels of 10% or more in 3 or more measurements over 2 weeks

2. Initial workup of GTN should include all of the following except
   A. chest x-ray
   B. brain MRI
   C. CT of the abdomen and pelvis
   D. biopsy of suspicious lesions in the vagina

3. A 30-year-old woman is diagnosed with GTN. She delivered a full-term infant 1 year ago and has not been pregnant since then. Her initial serum β-hCG level is 90,000 mIU/mL. Ultrasonography of the pelvis demonstrates a 4-cm intrauterine mass. A chest x-ray reveals 2 lesions that seem to be pulmonary metastases. Which one of the following reflects her stage and score?
   A. I:4
   B. III:8
   C. III:10
   D. I:7

4. Metastases seen only on chest CT have significant prognostic value and should be included in determination of stage.
   A. True
   B. False

5. A patient has been diagnosed with low-risk, stage I:1 GTN. Initial consideration for management may include
   A. single-agent therapy with methotrexate
   B. single-agent therapy with actinomycin D
   C. repeat dilation and curettage
   D. all of the above

6. In the setting of failed EMA-CO therapy for patients with high-risk disease, the most commonly recommended regimen is
   A. EMA-EP
   B. carboplatin and paclitaxel
   C. Doxil and bevacizumab
   D. whole pelvic radiation with cisplatin

7. Hysterectomy for GTN reduces the number of chemotherapy cycles to achieve remission.
   A. True
   B. False

8. PSTT and ETT differ from other types of GTN in which of the following ways?
   A. Staging criteria
   B. Hysterectomy as first step in management
   C. Resistance to chemotherapy
   D. B and C

9. All of the following are significant risk factors for poor prognosis in patients with nonmetastatic PSTT and ETT except
   A. deep myometrial invasion
   B. antecedent pregnancy interval
   C. tumor necrosis
   D. serum hCG level higher than 10,000 mIU/mL

10. PSTT and ETT can be reliably diagnosed and monitored using hCG level as a tumor marker.
    A. True
    B. False