Gestational Trophoblastic Disease (GTD) — Symptoms and Treatment

GTD are diseases that arise from aberrant fertilization tissue within the maternal host and are identified early due to markedly elevated hCG levels and characteristic ultrasound findings. Uterine evacuation is the recommended treatment, while chemotherapy can be reserved for patients with recurrent disease or neoplastic GTD.

Background and Definitions of Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) is a spectrum of placental disorders resulting from abnormal placental trophoblastic growth that comprises from benign molar pregnancies (complete and partial) through to the neoplastic conditions such as invasive mole, choriocarcinoma and placental site trophoblastic tumor (PSTT) depending on their aggressiveness and invasiveness.

The following discussion is limited to the molar pregnancies unless otherwise mentioned.
Epidemiology of Gestational Trophoblastic Disease

The incidence of molar pregnancy is estimated to be 1 in 1,200 live births in the United States. Since this is a disease of pregnancy, it only occurs in women. Its incidence increases in the extremes of ages with the increasing maternal age being the single most significant risk factor for GTD and the risk increases 5—10 times after the age of 40 years. It is also common in teenage pregnancies. Parity, however, does not increase the risk.

The incidence is higher in Asia at a rate of 1 in 500—600 pregnancies. Complete moles are more common than the incomplete type.

Risk Factors of Gestational Trophoblastic Disease

- The past history of molar pregnancy puts the patient at a 10-times higher risk of developing a recurrent GTD
- History of previous spontaneous abortions and infertility also increase the risk of GTD
- Low socioeconomic status
- Protein, folic acid and carotene deficiency
- The neoplastic GTDs are rare and may develop after a molar pregnancy, a non-molar pregnancy or a live birth. The incidence is estimated to be approximately 1 in 50,000 live births

Pathophysiology of Gestational Trophoblastic Disease

The molar pregnancies are divided into complete and partial moles. This distinction is based on gross pathology, histopathology and karyotyping.

Complete moles are diploid in nature and paternal in origin. They are formed when an “empty” anuclear ovum gets fertilized by either one sperm giving the solely paternal 46XX karyotype, or by two sperms giving the less common 46XY karyotype. They do not contain fetal tissue. Other features of complete moral pregnancy are described in Table 1.

Partial moles are triploid in origin. They are formed when a normal ovum is fertilized by two sperms hence they contain two sets of paternal genes and one set of maternal genes. They contain fetal tissue. The other features of partial molar pregnancy are described in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete Molar Pregnancy</th>
<th>Partial Molar Pregnancy</th>
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<tbody>
<tr>
<td>Karyotype</td>
<td>Diploid: Parenteral 46XX in 87%, Parenteral 46XY in 13%</td>
<td>Triploid: Two sperms with one ovum</td>
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<tr>
<td>Immunohistochemistry</td>
<td>Absent p57 and PHLDA2</td>
<td>Present p57 and PHLDA2</td>
</tr>
<tr>
<td>Presence of fetal tissues</td>
<td>Absent</td>
<td>Present but highly malformed</td>
</tr>
<tr>
<td>Human chorionic gonadotropin</td>
<td>Markedly elevated</td>
<td>Usually not elevated</td>
</tr>
<tr>
<td>Villous edema</td>
<td>Severe</td>
<td>Mild</td>
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Additional, overexpression of the epidermal growth factor receptors and matrix metalloproteinases (MMPs), which module cell-to-matrix interactions, have been described in the pathogenesis of GTDs.

In cases of neoplastic GTDs, p53 mutations have been identified in the histopathological examination of GTD biopsies, similar to other forms of cancer. Other oncogenes known to be associated with GTD include c-myc, bcl-2, Rb, and p21.

Clinical Presentation of Gestational Trophoblastic Disease

The classic clinical presentation of molar pregnancy includes features such as:

- Hyperemesis (severe nausea and vomiting)
- First trimester vaginal bleeding
- Enlarged uterus (large for gestational age) in a woman of childbearing age

Other features suggestive of gestational trophoblastic disease include:

- Absence of fetal heart tones and fetal structures in advanced gestation
- Elevated β-HcG titers
- Per vaginal expulsion of vesicles
- Theca lutein cysts seen
- Early onset preeclampsia

All clinicians need to be aware of these signs and symptoms and should immediately order a pregnancy test.

Rarely women with GTDs may present with clinical features of hyperthyroidism, abdominal distension and/or early onset pre-eclampsia. Since the human chorionic gonadotropin (hCG) has structural homology with thyroid stimulating hormone (TSH), the elevated levels of hCG in women with GTDs may have thyrotropic actions.

Very rarely, women with GTDs can present with seizures, altered mental status or acute
respiratory failure, often secondary to the metastatic disease.

Diagnostic Workup

The single and the most important test for the diagnosis of GTD is the assessment of human chorionic gonadotropin levels (hCG) levels, which are greatly elevated for the gestational age. Additionally, the level of elevation in hCG can also be predictive of the outcome in patients with GTD. The hCG correlates well with the volume of the trophoblastic tissue and larger aggressive tumors have the higher hCG levels.

The next diagnostic step is ultrasonography. It helps in pre-evacuation diagnosis but the definitive diagnosis is made by histological examination.

Gestational trophoblastic diseases appear as a snowstorm appearance within the uterine cavity with multiple hypoechoic areas corresponding to villi and missing fetus or gestational sac.

Nowadays, the use of ultrasonography in early pregnancy has resulted in earlier diagnosis of molar pregnancies even before the development of classic clinical features.

The complete moles have marked chorionic villi edema and swelling, which is evident on ultrasound examination, and there is no fetal tissue. In patients with partial moles, there are focal cystic changes in the placenta and highly deformed fetal tissue.

A chest X-ray should be advised whenever a molar pregnancy is diagnosed to look for metastatic spread, as the lungs are the most common primary sites of metastasis for neoplastic GTDs. Histopathological examination and karyotyping provide more information about the type of the GTD and can affect the management plan and prognosis of the patient. The Table 1 above describes the most commonly identified features of complete versus partial molar pregnancy, including histopathological and karyotyping differences.

Treatment of Gestational Trophoblastic Disease

The standard treatment for GTDs is the uterine evacuation. The suction curettage is recommended for both complete and partial molar pregnancies especially when fertility preservation is desired by the patient. The medical evacuation (with mifepristone and misoprostol) can be used in some cases of partial molar pregnancy when the size of the fetal parts preclude the use of suction curettage.

Prophylactic actinomycin-D is used following the evacuation of a complete molar pregnancy to reduce the risk of future neoplastic GTDs.

When future fertility is not a concern, a hysterectomy is indicated which removes the risk of local recurrence. Unfortunately, a hysterectomy does not prevent metastatic disease and early diagnosis is essential to prevent metastasis.

GTDs are highly vascular tumors and intense bleeding can occur during or after the evacuation. The intravenous oxytocin may be used to facilitate uterine contraction and reduce the risk of uterine bleeding. The Rh-negative women should receive Rh immune globulin.

The neoplastic GTDs are encountered in up to 28% of the patients with complete moles after evacuation.
The prediction of the risk of developing neoplastic GTD is dependent on the following factors:

1. An hCG level above 100,000 mIU/ml
2. Presence of theca lutein cysts in the ovaries
3. Severe uterine enlargement.

Accordingly, after evacuation, patients should be followed up with a **weekly hCG assessment until hCG is normalized in at least three consecutive measurements**. Once hCG levels are normalized then they should be checked monthly for 6 months. The levels of hCG should be in decreasing trend and should never increase. If hCG levels rise anytime during the follow-up, the metastatic disease should be excluded.

During the follow-up, the contraceptive methods are advised to prevent pregnancy. Since pregnancy causes the hCG levels to rise, it will disturb the follow-up process and increases the risk of future GTDs.

The barrier methods of contraception are advised until hCG levels are normalized. Afterward, OCPs may be used. The intrauterine contraceptive devices should be discouraged in early stages to reduce the risk of uterine perforation.

Patients, whose hCG levels are not normalized, are candidates for chemotherapy.

**References**


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