Gestational Trophoblastic Disease (GTD) — Symptoms and Treatment

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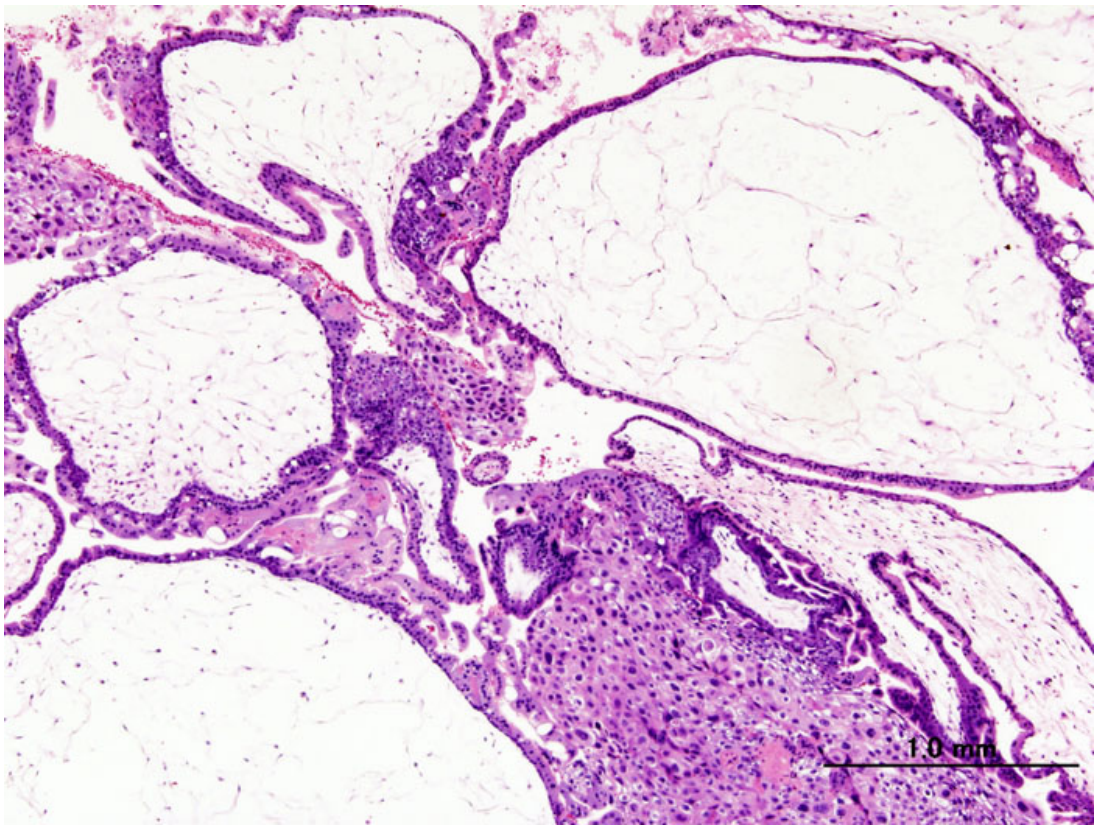
GTD are diseases that arise from aberrant fertilization tissue within the maternal host and are identified early due to markedly elevated hCG levels and characteristic ultrasound findings. Uterine evacuation is the recommended treatment, while chemotherapy can be reserved for patients with recurrent 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,** ranging from benign molar pregnancies (complete and partial) to 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. The incidence is higher in Asia, at a rate of 1 in 500—600 pregnancies. Complete moles are more common than the incomplete type. Since this is a disease of pregnancy, it only occurs in women. Its incidence increases in the extremes of ages. Increasing maternal age is 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.

Risk Factors of Gestational Trophoblastic Disease

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

Pathophysiology of Gestational Trophoblastic Disease

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, either by 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.

Characteristic	Complete Molar Pregnancy	Partial Molar Pregnancy
Karyotype	Diploid: Parenteral 46XX in 87%, Parenteral 46XY in 13%	Triploid: Two sperms with one ovum
Immunohistochemistry	Absent p57 and PHLDA2	Present p57 and PHLDA2
Presence of fetal tissues	Absent	Present but highly malformed
Human chorionic gonadotropin level	Markedly elevated	Usually not elevated
Villous edema	Severe	Mild
Risk of Gestational Trophoblastic Neoplasia	28% of the cases	4% of the cases

Table 1: a comparison between complete and partial molar pregnancy, the two

most common forms of gestational trophoblastic disease.

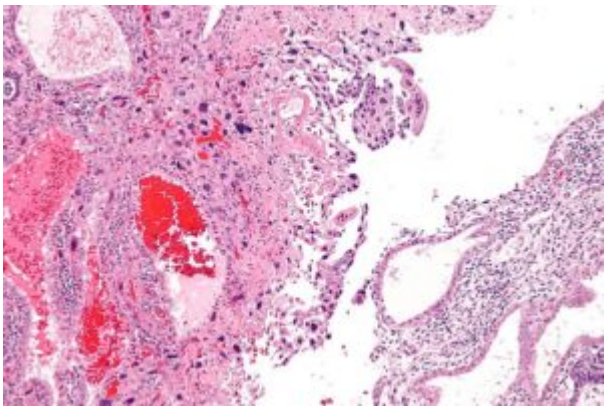


Image: “Intermediate magnification micrograph of intermediate trophoblasts, in a case of a complete hydatidiform mole. H&E stain.” by Nephron – Own work. License: CC BY-SA 3.0

Additionally, **overexpression of the epidermal growth factor receptors** and **matrix metalloproteinases (MMPs),** which module cell-to-matrix interactions, have been described in GTD pathogenesis.

In cases of neoplastic GTDs, there are **p53 mutations** 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 suggesting GTD include:

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

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

In rare instances, 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), 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 hCG level can help predict outcomes in patients with GTD. The hCG correlates well with the volume of the trophoblastic tissue; larger, aggressive tumors have higher hCG levels.

The next diagnostic step is **ultrasonography**. It helps with pre-evacuation diagnosis, but the definitive diagnosis is made by histological examination. GTDs have a snowstorm appearance within the uterine cavity, with multiple hypoechoic areas, corresponding to villi and a missing fetus or gestational sac.

Ultrasonography in early pregnancy leads to earlier diagnoses of molar pregnancies even before the development of classic clinical features.

Complete moles have marked **chorionic villi edema and swelling**, which is evident on ultrasound examination, and there is no fetal tissue. Patients with partial moles will have 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. The lungs are the most common primary site of metastasis for neoplastic GTDs.

Histopathological examination and **karyotyping** provide more information about the type of GTD, which can affect the management plan and the patient's prognosis. 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

Uterine evacuation is the standard treatment for GTDs. Suction curettage is recommended for both complete and partial molar pregnancies, especially when the patient is concerned with fertility preservation. The medical evacuation (with mifepristone and misoprostol) can be used in some cases of partial molar pregnancy when the size of the fetal parts precludes suction curettage. **Prophylactic actinomycin-D** is used after 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;** early diagnosis is essential to prevent metastasis.

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

Neoplastic GTDs are encountered in up to 28% of the patients with complete moles after evacuation.

The risk of developing neoplastic GTD depends 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 an 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, they should be checked monthly for six months. The hCG levels should decrease; if they increase anytime during the follow-up, the metastatic disease should be ruled out.

During follow-up, patients who have not undergone hysterectomy should use barrier contraceptive methods 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. After hCG levels are normalized, patients may use OCPs. 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

Garner EIO, Goldstein DP, Feltmate CM, Berkowitz RS (2007) Gestational trophoblastic disease. Clin Obstet Gynecol 50:112–22. doi: 10.1097/GRF.0b013e31802f17fc

Notes