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Gestational trophoblastic disease

Background
Gestational trophoblastic disease (GTD) is a spectrum of tumors with a wide range of biologic behavior and potential for metastases. GTD refers to both the benign and malignant entities of the spectrum and includes hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumor. The last three are termed gestational trophoblastic tumors (GTT); all may metastasize and are potentially fatal if untreated.

The incidence of hydatidiform mole varies in different regions of the world but has been falling. In North America the incidence is approximately 0.6 to 1.1 per 1000 pregnancies; the rate is approximately three times higher in Asia. Choriocarcinoma in North America occurs in one of every 20,000 to 40,000 pregnancies.

The risk of repeat molar pregnancy in a conception following one molar pregnancy (complete, partial, or persistent GTN) is approximately 1 percent, which is increased compared with the 1:1000 risk of molar gestation in the general population. Therefore, ultrasound should be obtained in the late first trimester of subsequent pregnancies to confirm normal fetal development. Additionally, an hCG level should be obtained six weeks after completion of subsequent pregnancies to rule out occult choriocarcinoma. (see Management of Subsequent Pregnancies, below)

Routine pathologic evaluation of the placenta, while recommended in the past, is not necessary. However, products of conception should be evaluated by a pathologist following any spontaneous or therapeutic abortion. (See Management of Subsequent Pregnancies, below)

Risk factors for malignant complication at time of presentation
- -Significant uterine enlargement
- -HCG over 100,000 mIU/ml at diagnosis
- -Theca lutein cysts > 6 cm diameter
- -Hx of previous molar pregnancy
- -Maternal age greater than age 40
- -Post evacuation hemorrhage not due to incomplete evacuation

Molar Pregnancy (Hydatidiform mole)
Hydatidiform mole is classified as complete (CHM) or partial mole (PHM), which are distinguished by differences in clinical presentation, pathology, genetics, and epidemiology. The risk of malignant sequelae requiring therapy ranges from 8% to 15% with complete mole, to 1.5% to 6% with partial mole.

The most common symptom is vaginal bleeding, which occurs in 84% of patients with complete moles. Fifty percent of patients with CHM show uterine enlargement and high levels of human chorionic gonadotropin (hCG). In contrast, patients with partial mole present with signs and symptoms of an incomplete or missed abortion, and have bleeding, a small uterus, and low hCG levels.

Cytogenetic studies have characterized the two molar syndromes. In 90% of complete moles there are paternally derived chromosomes with a 46XX karyotype. Partial moles are most commonly due to a fertilization error in which a normal ovum is fertilized by two spermatozoa, resulting in a triploid karyotype (69XXY). Flow cytometry has been employed to differentiate the two molar types but is not widely available.

Diagnosis
The characteristic appearance of a vesicular molar pattern in CHM can often be identified in the first trimester before vaginal spotting or the passage of macroscopic vesicles. There is often no evidence of a fetus.

The early diagnosis of a partial mole is more complex and less likely, although ultrasound may demonstrate focal cystic spaces in the placenta and an increase in the transverse diameter of the gestational sac. A fetus may be seen in an advancing gestation.

Management

Chest X-ray	-Done at evacuation. Repeat at 4 wks. Or at any increasing titer.
Pelvic exam	-Perform at 1st & 4th week after evacuation.
Blood Type	-Treat if RhoGAM candidate.
Quantitative B-hCG	-Weekly until negative titer x3, then monthly for 3 months after negative
Contraception	-Defer pregnancy for at least 3 months after negative titer -LARC's preferred (see IUD comments below)

In both CHM and PHM, after diagnosis and workup, which includes a complete blood count (CBC), β-hCG, and chest X-ray, evacuation of the uterine contents is carried out by means of suction curettage followed by blunt curettage of the uterine cavity. Intravenous oxytocin is administered after the cervix is dilated and is continued for several hours postoperatively.

Rarely, in partial molar pregnancies, where the size of the fetus precludes suction curettage, medical termination may be used; these patients, however, may be at an increased risk of persistent trophoblastic disease.

In patients who desire surgical sterilization, an abdominal hysterectomy with the mole in situ can be considered if sterilization criteria have been met.

Routine repeat evacuation after the diagnosis of molar pregnancy is not warranted.

In twin pregnancies with a viable fetus and a molar pregnancy, the pregnancy may be allowed to continue with MFM and GYN Oncology consultation.

Careful follow-up is critical after evacuation of a molar pregnancy, to identify those at risk of developing malignant sequelae. Repeated weekly assays of hCG levels should be carried out until three negative levels are obtained, and then followed by monthly hCG levels times six, along with regular pelvic examinations. A chest X-ray is indicated if the β-hCG rises.

Contraceptive measures should be instituted, ideally using LARCs, and the patient advised to avoid pregnancy until hCG values have remained normal for 3 months after negative titer.

An IUD may be used in patients with confirmed GTD and undetectable or decreasing hCG levels. For patients with suspected intrauterine disease, an IUD should be used with caution, or consider other forms of contraception more strongly, e.g., combined estrogen-progestin. For patients with confirmed intrauterine disease and persistently elevated hCG levels, the Centers for Disease Control and Prevention recommends not inserting an intrauterine device (IUD) because of theoretical risk for perforation, infection, and hemorrhage.

Medical complications of molar pregnancy, including pregnancy-induced hypertension, hyperthyroidism, anemia, and hyperemesis gravidarum, are more frequently seen among patients with complete moles. Approximately 15–25% of patients with complete moles will have theca lutein cysts with ovarian enlargement of more than 6 cm. Malignant sequelae occur in less than 5% of patients with partial moles, compared with approximately 20% after evacuation of complete hydatidiform moles.

Pulmonary complications are frequently observed around the time of molar evacuation among patients with marked uterine enlargement. 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. 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. 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.

Follow-up Recommendations (see bulleted Management above)
-One provider / case manager should follow the patient, if possible
-Review lab data q month
-Verify ongoing contraception each visit until follow-up period completed
-See discussion of false-positive hCG values, also known as "phantom hCG" (Appendix 1)

Indication for further treatment

-Plateauing of beta-hCG levels over at least three weeks ($\pm$ 10%)
-Titer greater than 20,000 mIU/ml at 4 weeks post evacuation
-Titer not less than 4 mIU/ml by 12 weeks post evacuation
-Elevated titer after reaching normal levels (r/o pregnancy)

Persistent hCG
If the patient is low risk by the WHO Scoring System, below, then she can be treated in the following manner.

-MTX 50 mg/m^2 IM weekly until the serum beta-hCG concentration falls to normal (less than 5 mIU/mL) for three consecutive weeks

TABLE 1: WHO SCORING SYSTEM

	0	1	2	4
AGE	≤ 39	> 39		
Antecedent pregnancy	Hydatid. mole	Abortion	Term pregn.	
Interval months from index pregnancy	4	4–6	7–12	>12
Pretreatment hCG (IU/mL)	<10^3	10^3–10^4	10^4–10^5	>10^5
Largest tumor size including uterus		3–4 cm	5 cm	
Site of metastases		spleen, kidney	GI tract	brain, liver
Number of metastases identified		1–4	4–8	> 8
Previously failed chemotherapy			single drug	$\geq$ 2 drugs

WHO Scoring System

Low risk	WHO Score: 4 or less
Moderate risk	WHO Score: 5-7
High risk	WHO Score: 8 or greater

Indication for Gyn Oncology consultation
-Moderate or high risk by WHO Scoring System
-Tissue diagnosis of choriocarcinoma

-Evidence of metastases (chest x-ray, pelvic exam)
-Persistence of hCG after initial chemotherapy regimen above
-Persistence of beta-hCG six months after molar evacuation

Management of subsequent pregnancies
-Estimates of the risk of recurrent HM are: after one molar pregnancy (1 to 1.9 percent), and after two molar pregnancies (15 to 17.5 percent).
-Ultrasound should be obtained in the late first trimester of subsequent pregnancies to confirm normal fetal development
-An hCG level should be obtained six weeks after completion of subsequent pregnancies to rule out occult choriocarcinoma
-Routine pathologic evaluation of the placenta, while recommended in the past, is NOT necessary. However, products of conception should be evaluated by a pathologist following any spontaneous or therapeutic abortion.

References:

Avoiding inappropriate clinical decisions based on false-positive human chorionic gonadotropin test results. ACOG Committee Opinion No. 278. American College of Obstetricians and Gynecologists. Obstet Gynecol 2002;100:1057-9. (Re-affirmed 2020)

ACOG Endorsed:
Epidemiology, Diagnosis, and Treatment of Gestational Trophoblastic Disease: A Society of Gynecologic Oncology Evidenced-based Review and Recommendation. Gynecol Oncol 2021. doi: 10.1016/j.ygyno.2021.10.003. (Endorsed October 2021)

JOINT GOC / SOGC CLINICAL PRACTICE GUIDELINE
Guideline No. 408: Management of Gestational Trophoblastic Diseases. Eiriksson L, et al. Journal of Obstetrics and Gynaecology Canada, 2021 (Jan) Vol. 43:1, 91–105 (Accessed 12/10/22)

Wang Q, Fu J, Hu L, Fang F, Xie L, Chen H, He F, Wu T, Lawrie TA. Prophylactic chemotherapy for hydatidiform mole to prevent gestational trophoblastic neoplasia. Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD007289. DOI: 10.1002/14651858.CD007289.pub3. (Accessed 12/10/22)

Berkowitz RS, Im SS, Bernstein MR, Goldstein DP. Gestational trophoblastic disease: subsequent pregnancy outcome, including repeat molar pregnancy. J Reprod Med 1998;43:81–6

Berkowitz RS,Goldstein DP. Chorionic tumours. N Engl J Med 1996;335:1740-8.

Medical eligibility criteria for contraceptive use. CDC and Prevention
https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html (Accessed 12/10/22)

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Appendix 1
Characteristics of false-positive hCG values, also known as "phantom hCG"

1. 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.

2. Most patients with false-positive hCG values have low-level hCG elevations, 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. Many of these patients have an undefined previous pregnancy event and do not have radiographic evidence of metastatic disease.

3. 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.
4. 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.

5. 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. 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.

6. 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. 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.