Gestational trophoblastic disease (GTD) is a spectrum of cellular proliferations arising from the placental villous trophoblast encompassing 4 main clinicopathologic forms: hydatidiform mole (complete and partial), invasive mole, choriocarcinoma, and placental site trophoblastic tumor (PSTT) (Table). The term “gestational trophoblastic neoplasia” (GTN) has been applied collectively to the latter 3 conditions, which can progress, invade, metastasize, and lead to death if left untreated.

GTD was historically associated with significant morbidity and mortality. Hydatidiform moles were often accompanied by serious bleeding and other medical complications prior to the development of early detection and effective uterine evacuation means in the 1970s. The outcomes for GTN were likewise poor before the introduction of chemotherapy into their management 50 years ago. The mortality rate for invasive mole approached 15%, most often because of hemorrhage, sepsis, embolic phenomena, or complications from surgery. Choriocarcinoma had a mortality rate of almost 100% when metastases of widespread metastatic disease were present and approximately 60% even when hysterectomy was done for apparent nonmetastatic disease. Gestational trophoblastic neoplasms are now some of the most curable of all solid tumors, with cure rates >90% even in the presence of widespread metastatic disease.1–3

Epidemiology
The incidence and etiologic factors contributing to the development of GTD have been difficult to characterize. The problems in accumulating reliable epidemiologic data can be attributed to a number of factors, such as inconsistencies in case definitions, inability to adequately characterize the population at risk, no centralized databases, lack of well-chosen control groups against which to compare possible risk factors, and rarity of the diseases.4

Epidemiologic studies have reported wide regional variations in the incidence of hydatidiform mole.5 Estimates from studies conducted in North America, Australia, New Zealand, and Europe have shown the incidence of hydatidiform mole to range from 0.57–1.1 per 1000 pregnancies, whereas studies in Southeast Asia and Japan have suggested an incidence as high as 2.0 per 1000 pregnancies.6–8 Investigations into possible ethnic and racial differences leading to an increased incidence of hydatidiform mole among American Indians, Eskimos, Hispanics, and African Americans as well as various Asian populations have not been able to attribute them to genetic traits, cultural factors, or simply differences in reporting.7–9

Data with respect to choriocarcinoma incidence rates are even more limited. Collection of data on the incidence of choriocarcinoma has been more difficult not only for reasons similar to those encountered with hydatidiform moles, but also because of the rarity of choriocarcinoma and the difficulty in clinically distinguishing postmolar choriocarcinoma from invasive mole. In Europe and North America, choriocarcinoma affects approximately 1 in 40,000 pregnancies and 1 in 40 hydatidiform moles, whereas in Southeast Asia and Japan choriocarcinoma rates are higher at 9.2 and 3.3 per 40,000 pregnancies, respectively. The incidence rates of both hydatidiform mole and choriocarcinoma have declined over the past 50 years in all populations.10,11 Several potential etiologic risk factors have been evaluated for the development of complete hydatidiform mole.12 The 2 established risk factors that have emerged are extremes of maternal age and prior molar pregnancy. Advanced or very young maternal age has consistently correlated with higher rates of complete hydatidiform mole. Compared

Key words: chemotherapy, choriocarcinoma, gestational trophoblastic disease, gestational trophoblastic neoplasia, hydatidiform mole
Fat dietary intake and the incidence of
pared to women without a history of
creased risk of a molar pregnancy com-
tion, giving women a 2- to 3-fold in-
the risk for the general population.15,16

The risk of repeat molar pregnancy after
mole is 1.9 times higher for
years.13,14 Prior hydatidiform mole pre-
issues to another molar pregnancy.
The risk of repeat molar pregnancy after
mole is about 1%, or about 10-20 times the risk for the general population.15,16

Familial clusters of biparental complete
hydatidiform moles associated with
omal pregnancy.13,14 Prior hydatidiform mole pre-
disposes to another molar pregnancy.
women aged 21-35 years, the risk of
complete mole is 1.9 times higher for
women both >35 years and <21 years as
well as 7.5 times higher for women >40

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Pathology
Molar pregnancies and gestational trophoblastic neoplasms all take their origin
placed trophoblast. Normal trophoblast is composed of cytotrophoblast, syncytiotrophoblast, and intermediate trophoblast. Syncytiotrophoblast invades the endometrial stroma with implantation of the blastocyst and is the cell
type that produces human chorionic gonadotropin (hCG). Cytotrophoblast functions to supply the syncytiotrophoblast with cells in addition to forming outgrowths that become the chorionic villi covering the chorionic sac. The villous choriocarcinoma is approximately 1000

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times more likely after a complete mole than after another pregnancy event. The
risk is also increased in women of Asian and American Indian descent as well as African Americans. Similar to molar pregnancies, the median age of women with choriocarcinoma is higher than that for normal pregnancies.11 There also seems to be an increased risk of choriocarcinoma in
women with long-term oral contraceptive use and blood group A.5,20

### TABLE
Clinicopathologic features of gestational trophoblastic disease

<table>
<thead>
<tr>
<th>Gestational trophoblastic disease</th>
<th>Pathologic features</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydatidiform mole, complete</td>
<td>46,XX (mainly); 46,XV Absent fetus/embryo Diffuse swelling of villi Diffuse trophoblastic hyperplasia</td>
<td>15-20% trophoblastic sequelae hCG often &gt;100,000 mIU/mL Medical complications</td>
</tr>
<tr>
<td>Hydatidiform mole, partial</td>
<td>Triplet (69, XXX; 69, XXY; 69 XXX) Abnormal fetus/embryo Focal swelling of villi Focal trophoblastic hyperplasia</td>
<td>&lt;5% trophoblastic sequelae hCG usually &lt;100,000 mIU/mL Rare medical complications</td>
</tr>
<tr>
<td>Invasive mole</td>
<td>Myometrial invasion Swollen villi Hyperplastic trophoblast</td>
<td>15% metastatic–lung/vagina Most often diagnosed clinically, rather than pathologically</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Abnormal trophoblastic hyperplasia and anaplasia Absent villi Hemorrhage, necrosis</td>
<td>Vascular spread to distant sites—lung/brain/liver Malignant disease</td>
</tr>
<tr>
<td>PSTT</td>
<td>Tumor cells infiltrate myometrium with vascular/lymphatic invasion Intermediate cells/absent villi Less hemorrhage and necrosis Tumor cells stain positive for hPL</td>
<td>Extremely rare hCG levels less reliable indicator Relatively chemoresistant Mainly surgical treatment</td>
</tr>
</tbody>
</table>

hCG, human chorionic gonadotropin; hPL, human placental lactogen; PSTT, placental site trophoblastic tumor.

In the absence of an ascertainable fetus or embryo, the trophoblast is consistently hyperplastic with varying degrees of atypia, and villous capillaries are absent (Figure 1). Approximately 90% of complete moles are 46, XX, originating from duplication of the chromosomes of a haploid sperm after fertilization of an egg in which the maternal chromosomes are either inactive or absent. The other 10% of complete moles are 46, XY, or 46, XX, as a result of fertilization of an empty ovum by 2 sperm (dispermy). Trophoblastic neoplasia (invasive mole or choriocarcinoma) follows complete mole in 15-20% of cases.23-27 Partial hydatidiform moles demonstrate identifiable fetal or embryonic tissue, chorionic villi with focal edema that vary in size and shape, scalloping and prominent stromal trophoblastic inclusions, and a functioning villous circulation, as well as focal trophoblastic hyperplasia with mild atypia only (Figure 2). Most partial moles have a triploid karyotype (usually 69, XXY), resulting from the fertilization of an apparently normal ovum by 2 sperm. Less than 5% of partial moles will develop postmolar GTN; metastases occur rarely and a histopathologic diagnosis of choriocarcinoma has not been confirmed after a partial mole.23,24,27-30

**Invasive mole**

Invasive mole is a benign tumor that arises from myometrial invasion of a hydatidiform mole via direct extension through tissue or venous channels (Figure 3). Approximately 10-17% of hydatidiform moles will result in invasive mole, and about 15% of these will metastasize to the lungs or vagina. Invasive mole is most often diagnosed clinically rather than pathologically based on persistent hCG elevation after molar evacuation and is frequently treated with chemotherapy without a histopathologic diagnosis.31

**Choriocarcinoma**

Choriocarcinoma is a malignant disease characterized by abnormal trophoblastic hyperplasia and anaplasia, absence of chorionic villi, hemorrhage, and necrosis (Figure 4), with direct invasion into
the myometrium and vascular invasion resulting in spread to distant sites, most commonly to the lungs, brain, liver, pelvis and vagina, kidney, intestines, and spleen. Choriocarcinoma has been reported to occur in association with any pregnancy event. Approximately 25% of cases follow abortion or tubal pregnancy, 25% are associated with term or preterm gestation, and the remaining 50% arise from hydatidiform moles, although only 2-3% of hydatidiform moles progress to choriocarcinoma.32

Placental site trophoblastic tumor
PSTT is an extremely rare disease that arises from the placental implantation site and consists predominantly of mononuclear intermediate trophoblasts without chorionic villi infiltrating in sheets or cords between myometrial fibers (Figure 5). PSTT is associated with less vascular invasion, necrosis, and hemorrhage than choriocarcinoma, and it has a propensity for lymphatic metastasis. Immunohistochemical staining reveals the diffuse presence of cytokeratin and human placental lactogen, whereas hCG is only focal. Cytogenic studies have revealed that PSTTs are more often diploid than aneuploid. Most PSTTs follow nonmolar gestations.35

Epithelioid trophoblastic tumor
Epithelioid trophoblastic tumor (ETT) is a rare variant of PSTT that simulates carcinoma. Based on morphologic and histochemical features, it appears to develop from neoplastic transformation of chorionic-type intermediate trophoblasts. Most ETTs present many years after a full-term delivery.34,35

Clinical presentation
Complete hydatidiform mole
Complete hydatidiform mole most commonly presents with vaginal bleeding, usually occurring at 6-16 weeks of gestation in 80-90% of cases. The other classic clinical signs and symptoms, such as uterine enlargement greater than expected for gestational dates (28%), hyperemesis (8%), and pregnancy-induced hypertension in the first or second trimester (1%), occur less frequently in recent years because of earlier diagnosis as a result of widespread use of ultrasonography and accurate tests for hCG. Bilateral theca lutein cyst enlargement of the ovaries occurs in approximately 15% of cases, hCG levels are often >100,000 mIU/mL, and fetal heart tones are absent.36-39

Partial mole
Partial mole does not have the same presenting features as complete mole. More than 90% of patients with partial moles have symptoms of incomplete or missed abortion, and the diagnosis is usually made after histologic review of curettage specimens. The main presenting symptom is vaginal bleeding, which occurs in approximately 75% of patients. Excessive uterine enlargement, hyperemesis, pregnancy-induced hypertension, hyperthyroidism, and theca lutein cysts develop infrequently. Preevacuation hCG levels are >100,000 mIU/mL in <10% of patients with partial moles.40-42

Gestational trophoblastic neoplasia
GTN has a varied presentation depending on the antecedent pregnancy event, extent of disease, and histopathology. Postmolar GTN (invasive mole or choriocarcinoma) most commonly presents as irregular bleeding following evacuation of a hydatidiform mole. Signs suggestive of postmolar GTN are an enlarged, irregular uterus and persistent bilateral ovarian enlargement. Occasionally, a metastatic vaginal lesion may be noted on evacuation, disruption of which may cause uncontrolled bleeding. Choriocarcinoma associated with nonmolar gestation has no characteristic symptoms or signs, which are mostly related to invasion of tumor in the uterus or at metastatic sites. In patients with postpartum uterine bleeding and subinvolution, GTN should be considered along with other possible causes, such as retained products of conception or endomyometritis, primary or metastatic tumors of other organ systems, or another pregnancy occurring shortly after the first. Bleeding as a result of uterine perforation or metastatic lesions may result in abdominal pain, hemoptysis, melena, or evidence of increased intracranial pressure from intracerebral hemorrhage leading to headaches, seizures,
or hemiplegia. Patients may also exhibit pulmonary symptoms, such as dyspnea, cough, and chest pain, caused by extensive lung metastases. PSTTs and ETTs almost always cause irregular uterine bleeding often distant from a preceding nonmolar gestation, and rarely virilization or nephrotic syndrome. The uterus is usually symmetrically enlarged, and serum hCG levels are only slightly elevated.

Diagnosis
Ultrasonography
Ultrasonography plays a critical role in the diagnosis of both complete and partial mole, and it has virtually replaced all other means of preoperative diagnosis. Because the chorionic villi of complete moles exhibit diffuse hydropic swelling, a characteristic vesicular ultrasonographic pattern can be observed, consisting of multiples echoes (holes) within the placental mass and usually no fetus (Figure 6). Ultrasonography may also facilitate the early diagnosis of a partial mole by demonstrating focal cystic spaces within the placenta and an increase in the transverse diameter of the gestational sac.

Human chorionic gonadotropin
hCG is a disease-specific tumor marker produced by hydatidiform moles and gestational trophoblastic neoplasms. It is easily measured quantitatively in both urine and blood, and hCG levels have been shown to correlate with the burden of disease. It is a placental glycoprotein composed of 2 dissimilar subunits: an α subunit resembling that of the pituitary glycoprotein hormones and a β subunit that is unique to placental production. Several forms of hCG exist, including at least 6 major variants that can be detected in serum: hyperglycosylated, nicked, absent C-terminal of the β subunit, free β subunit, nicked free β subunit, and free α subunit. The hCG molecules in GTD are more heterogeneous and degraded than those in normal pregnancy, therefore, an assay that will detect all main forms of hCG and its multiple fragments should be used to follow up patients with GTD. Most institutions currently use rapid, automated radiolabeled...
beled monoclonal antibody sandwich assays that measure different mixtures of hCG-related molecules. 

Hydatidiform moles are commonly associated with markedly elevated hCG levels above those of normal pregnancy. Approximately 50% of patients with complete mole have preevacuation hCG levels >100,000 mIU/mL. A single hCG determination, however, is seldom helpful in differentiating complete mole from a normal intrauterine pregnancy, a multiple gestation, or a pregnancy complicated by diseases such as erythroblastosis fetalis or intrauterine infections that are associated with an enlarged placenta, because hCG levels are highest in the late first trimester of pregnancy at a time when a diagnosis of molar pregnancy is usually being considered. Partial moles, on the other hand, are most often not distinguished by such elevated hCG levels, >100,000 mIU/mL in <10% of patients.

A clinical diagnosis of postmolar GTN is most often made by the finding of rising or plateauing hCG levels following evacuation of a hydatidiform mole. Choriocarcinoma is usually diagnosed by the finding of an elevated hCG level, frequently in conjunction with the discovery of metastases, following other pregnancy events. PSTT and ETT are commonly associated with slightly raised hCG levels.

Although accurate measurements of hCG levels are invaluable in diagnosing and later monitoring GTD, some laboratory assays may yield false-positive hCG results. These so-called phantom hCG results, with levels reported as high as 800 mIU/mL, have led to treatment of healthy patients with unnecessary surgery and chemotherapy. The causes of these false-positive test results are proteolytic enzymes that produce nonspecific protein interference and heterophile (human antimouse) antibodies. These antibodies are found in 3-4% of healthy people and can mimic hCG immunoreactivity by linking and capturing tracer mouse IgG. There are 3 ways to determine whether hCG assays are falsely positive when there is a clinical suspicion of phantom hCG: (1) determine a urine hCG level, which should be negative because the interfering substances are not excreted in urine; (2) request serial dilution of the serum, which should not show a parallel decrease with dilution; and (3) send the serum and urine of the patient to an hCG reference laboratory. Additionally, there is some cross-reactivity of hCG with luteinizing hormone (LH), which may lead to falsely elevated low levels of hCG. Measurement of LH to identify this possibility and suppression of LH with oral contraceptive pills will prevent this problem.

“Quiescent gestational trophoblastic disease” is a term applied to a presumed inactive form of GTN that is characterized by persistent, unchanged low levels (<200 mIU/mL) of “real” hCG for at least 3 months associated with a history of GTD or spontaneous abortion, but without clinically detectable disease. The hCG levels do not change with chemotherapy or surgery. Subanalysis of hCG reveals no hyperglycosylated hCG, which is associated with cytotrophoblastic invasion. Follow-up of patients with presumed quiescent GTD reveals subsequent development of active GTN in about one-quarter, which is heralded by an increase in both hyperglycosylated hCG and total hCG. According to the International Society for the Study of Trophoblastic Disease 2001 recommendations for managing this condition, false-positive hCG resulting from heterophile antibodies or LH interference should be excluded, the patient should be thoroughly investigated for evidence of disease, immediate chemotherapy or surgery should be avoided, and the patient should be monitored long term with periodic hCG testing while avoiding pregnancy. Treatment should be undertaken only when there is a sustained rise in hCG or the appearance of overt clinical disease.

Pathologic diagnosis
Pathologic diagnosis of complete and partial moles is made by examination of curettage specimens. Immunohistological staining for p57 (a paternally imprinted, maternally expressed gene) can differentiate absent immunostaining complete moles from positively staining hydropic abortuses and partial moles.
and flow cytometry can distinguish diploid from complete triploid partial moles.56,57 Additionally, pathologic diagnosis of invasive mole, choriocarcinoma, PSTT, and ETT can sometimes be made by curettage, biopsy of metastatic lesions, or examination of hysterectomy specimens or placentas. Biopsy of a vaginal lesion suggestive of a gestational trophoblastic tumor is dangerous because of the massive bleeding that may occur. 58

Hydatidiform mole

Treatment

Once the diagnosis of molar pregnancy is suspected by history, physical examination, hCG levels, and ultrasound findings, the patient should be evaluated for the presence of medical complications (anemia, preeclampsia, hyperthyroidism) by way of vital signs and laboratory tests, such as complete blood cell counts, basic chemistry, hepatic and thyroid panels, urinalysis, and chest x-ray. The preoperative evaluation should also include blood type and crossmatch, serum hCG level, and electrocardiogram if appropriate. After the diagnosis is confirmed and the patient is determined to be hemodynamically stable, the most appropriate method of molar evacuation should be decided upon.59,60

Suction evacuation and curettage is the preferred method of evacuation of a hydatidiform mole, independent of uterine size, for patients who wish to maintain their fertility.61,62 After anesthesia is achieved, the cervix is dilated to allow a 12- to 14-mm suction cannula to pass into the lower uterine segment. The cannula is then rotated as the intraluminal contents are removed. It is recommended that an intravenous oxytocin infusion be started at the onset of suction curettage and continued for several hours postoperatively to enhance uterine contractability. Suction evacuation should be followed by gentle sharp curettage. Because the risk of bleeding increases with uterine size, at least 2 U of blood should be immediately available when the uterus is >16-weeks’ gestational size. Attention to blood and crystalloid replacement decreases pulmonary complications. It is clear that with judicious use of appropriate equipment, access to blood products, careful intraoperative monitoring, and early anticipation of complications patient outcome improves. Patients who are Rh negative should receive Rh immune globulin at the time of evacuation, as Rh D factor is expressed on trophoblastic cells.59,60

Hysterectomy is an alternative to suction curettage if childbearing has been completed. The adnexa may be left intact even in the presence of theca lutein cysts. In addition to evacuating the molar pregnancy, hysterectomy provides permanent sterilization and eliminates the risk of local myometrial invasion as a cause of persistent disease. Because of the potential for metastatic disease even after hysterectomy, the risk of postmolar GTN still remains at 3-5%, thereby requiring continued hCG follow-up.61

Medical induction of labor and hysterotomy are not recommended for molar evacuation. These methods increase maternal morbidity, such as blood loss, incomplete evacuation requiring dilation and curettage, and the requirement for cesarean delivery in subsequent pregnancies. They also increase trophoblastic dissemination and the development of postmolar GTN requiring chemotherapy.62

A twin pregnancy consisting of a complete mole and a coexisting normal fetus is estimated to occur once in every 22,000-100,000 pregnancies. It must be distinguished from a partial mole (triploid pregnancy with fetus). The diagnosis can usually be established by ultrasound, but cytogenetics may be used to differentiate between chromosomally normal, potentially viable fetuses and triploid nonviable fetuses. Patients with a twin normal fetus/complete mole pregnancy should be cautioned that they may be at increased risk for hemorrhage and medical complications as well as development of persistent GTN. Suction evacuation and curettage in the operating room is recommended for desired pregnancy termination, bleeding, or complications, however, up to 40% of these pregnancies will result in normal viable fetuses if allowed to continue.63-66

Prophylactic administration of either methotrexate or actinomycin D chemotherapy at the time of or immediately after evacuation of a hydatidiform mole is associated with a reduction in incidence of postmolar GTN from approximately 15-20% down to 3-8%. The use of prophylactic chemotherapy should be limited, however, to special situations in which the risk of postmolar GTN is much greater than normal or where adequate hCG follow-up is not possible, as essentially all patients who are followed up with serial hCG testing after molar evacuation and found to have persistent GTN can be cured with appropriate chemotherapy.67-69

Follow-up after molar evacuation

Follow-up after evacuation of a hydatidiform mole is essential to detect trophoblastic sequelae (invasive mole or choriocarcinoma), which develop in approximately 15-20% with complete mole and 1-5% with partial mole.59,70-74 Clinical findings of prompt uterine involution, ovarian cyst regression, and cessation of bleeding are all reassuring signs, however, definitive follow-up requires serial serum quantitative hCG measurements every 1-2 weeks until 3 consecutive tests show normal levels, after which hCG levels should be determined at 3-month intervals for 6 months after the spontaneous return to normal. More than half of patients will have complete regression of hCG to normal within 2 months of evacuation. Contraception is recommended for 6 months after the first normal hCG result, to distinguish a rising hCG because of persistent or recurrent disease from a rising hCG associated with a subsequent pregnancy. The use of oral contraceptive pills is preferable because they have the advantage of suppressing endogenous LH, which may interfere with the measurement of hCG at low levels and studies have shown that they do not increase the risk of postmolar trophoblastic neoplasia.75-77 Pathologic examination of the placenta and other products of conception as well as determination of a 6-week postpartum hCG level is recommended with all future pregnancies.

The likelihood of persistent disease developing after evacuation of a complete mole increases with evidence of marked trophoblastic growth, such as a pre-
evacuation hCG level >100,000 mIU/mL, excessive uterine growth (>20-week size), and theca lutein cysts > 6 cm in diameter. Patients with ≥1 of these signs have approximately a 40% incidence of postmolar GTN compared to 4% for those without any of these signs. Patients with an age >40 years, a repeat molar pregnancy, an aneuploid mole, and medical complications of molar pregnancy, such as toxemia, hyperthyroidism, and trophoblastic embolization, are at increased risk for postmolar GTN.59

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