

EVERYONE'S GUIDE FOR CANCER THERAPY
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Trophoblastic Disease

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Gestational trophoblastic diseases (GTD) are disorders of abnormal growth of the placenta. They are always associated with a pregnancy. A key to understanding and managing patients with GTD is human chorionic gonadotropin (hCG) is a protein hormone produced by the placenta. It can be detected in the blood and urine and is an extremely sensitive indicator for GTD. It is measured often during both therapy and follow-up to measure the response to treatment and to detect recurrent disease.

Types There are four types of gestational trophoblastic disease: hydatidiform mole (also called a molar pregnancy), invasive mole (chorioadenoma destruens), gestational choriocarcinoma, and placental site trophoblastic disease. It is important to understand why the general term gestational trophoblastic disease (GTD) and the specific diseases hydatidiform mole (HM), chorioadenoma destruens (CD), and placental site trophoblastic disease (PSTT) co-exist. The specific disease requires biopsy material (tissue from the disease site) for microscopic examination to make the diagnosis. The disease sites may be difficult to reach without risk, i.e. hemorrhage or loss of fertility. Further human chorionic gonadotropic (hCG) is a reliable indicator of disease presence and status. Lastly, the managements of the specific diseases is the same stage for stage.

- A hydatidiform mole results from an abnormal embryo. There are two types of hydatidiform moles, complete and incomplete (partial). A complete mole usually has little or no fetal development and a large overgrowth of the placenta in the form of cysts or hydatid, hence the name hydatidiform mole (FR. MASS). The diagnosis of a complete hydatidiform mole is usually made during the first half of a pregnancy. A variety of clinical conditions may be confused with a molar pregnancy, but these can usually be distinguished on the basis of medical history, a physical exam and an ultrasound examination.

In contrast, a partial mole is associated with a fetus, placental tissue, umbilical cord and membranes. It occurs much less frequently than a complete mole. The fetus usually dies within nine weeks after the last menstrual period although occasionally it can survive to term.

Hydatidiform moles are sometimes associated with multiple ovarian cysts (theca-lutein cysts), high HCG titers, and pregnancy-induced hypertension. There is also the risk that the abnormal placental tissue will persist in the uterus or elsewhere in the body. These risks are greater for women with complete moles (10-20 percent) than those with partial moles (5-10 percent).

- An invasive mole (chorioadenoma destruens) is defined as a hydatidiform mole which persists and invades the uterine wall. It develops in 10 to 20 percent of all molar pregnancies.

- Choriocarcinoma is a cancer composed of only the cells which come from the placenta (trophoblastic cells). It differs from invasive mole which is made up of all the placental tissues. Furthermore, choriocarcinoma can follow any type of pregnancy, but an invasive mole can only follow a hydatidiform mole. About 50 percent of all cases of gestational choriocarcinoma follow a hydatidiform mole, 25 percent follow a spontaneous abortion or tubal pregnancy and 25 percent follow a normal term pregnancy. Choriocarcinoma follows a normal term pregnancy in 1 in 40,000 pregnancies. GTD after a normal pregnancy is always a choriocarcinoma, never a mole or an invasive mole.

What Causes It A hydatidiform or invasive mole occurs when a single sperm fertilizes an egg without a nucleus. The chromosomes in the sperm duplicate, resulting in an abnormal embryo that has only male genetic material. A mole can also occur when two sperm fertilize a single egg without a nucleus. A mole develops from the abnormally fertilized egg and is characterized by a lack of a normal fetus and by many small fluid-filled cysts.

The cause of choriocarcinoma is uncertain. It can arise from a normal pregnancy, a miscarriage, a tubal pregnancy or from either type of mole.

How It Spreads Hydatidiform moles generally stay confined to the uterus. When it begins to invade the wall of the uterus, it is called an invasive mole.

An invasive mole can penetrate the full thickness of the uterine wall and rupture, resulting in severe internal or vaginal bleeding. Invasive moles can also spread to other organs, most commonly to the vagina and the lung. This may be confusing since women with proven invasive moles who have metastases may also have choriocarcinoma. Although an invasive mole is more locally aggressive than a non-invasive mole, it is no more likely to develop into choriocarcinoma.

Choriocarcinoma can spread virtually anywhere in the body but most commonly spreads to the lung, the lower genital tract (cervix, vagina and vulva), the brain, liver, kidney and the gastrointestinal tract.

RISK FACTORS

Gestational trophoblastic disease occurs only in women of reproductive age. An invasive mole develops in 10 to 20 percent of all complete moles and 5 to 10 percent of all partial moles. Choriocarcinoma develops in three percent of complete moles but rarely in partial moles.

At Significantly Higher Risk

Risks for the development of a hydatidiform, invasive mole, or choriocarcinoma include:

- A prior mole (30 times the risk).
- Maternal age greater than 40 years (5 times) or less than 20 years (1.5 times).
- A previous spontaneous abortion (twice the risk).

At Slightly Lower Risk

- Eating a diet high in vitamin A and having one or more children without having a previous abortion is statistically correlated with a lower than average risk of developing a complete mole.

At Risk for Developing an Invasive Mole or Choriocarcinoma

For women with a molar pregnancy, there are several risk factors associated with the subsequent development of an invasive mole or choriocarcinoma. These include delayed hemorrhage after removal of the mole (D&C), large ovarian (theca-lutein) cysts, acute respiratory failure at the time of D&C, a large uterus before the D&C, a serum HCG level greater than 40,000 mIU/mL, a history of a previous mole and maternal age over 40.

SCREENING

GTD is not routinely screened for since it is so rare. An ultrasound examination early in any subsequent pregnancy to document a normal pregnancy is usually performed for women with prior GTD.

COMMON SIGNS AND SYMPTOMS

A molar pregnancy is often associated with absence of menses, symptoms of pregnancy, bleeding in the first half of a pregnancy, pain in the lower abdomen, high blood pressure before 24 weeks of pregnancy (10%), excessive nausea or vomiting, a uterus larger than normal for gestational age (50 percent of all cases), an absent fetal heartbeat and the expulsion of cysts.

Eighty to 90 percent of women with partial moles have abnormal uterine bleeding, the signs and symptoms of a spontaneous abortion, and a smaller than expected uterus for gestational age of the pregnancy.

The most common symptoms of choriocarcinoma are lack of menstrual period, symptoms of pregnancy, abnormal vaginal bleeding or pelvic pain. Women with liver metastases may have bleeding within the abdomen because of a ruptured liver. Those with metastases to the lung may have a dry cough, cough up blood and have chest pain or shortness of breath. Spread to the intestinal tract may also be associated with chronic blood loss and anemia or with massive hemorrhage. Brain metastases are often associated with symptoms that suggest a brain tumor or stroke.

DIAGNOSIS

The diagnosis is usually suspected after an ultrasound examination of the uterus, but absolute diagnosis of a mole is made by examining the cysts under a microscope. A serum HCG level far in excess of that of a normal pregnancy would support the diagnosis of a hydatidiform mole.

An invasive mole is seldom diagnosed definitively without a hysterectomy. The diagnosis is usually suggested after a hydatidiform mole is removed and the HCG titers remain persistently elevated and there is no evidence of metastases. It is more properly referred to as non-metastatic (confined to the uterus) trophoblastic disease (NMTD).

Confirmation of choriocarcinoma by removing cells for pathological analysis (biopsy) may be hazardous since this tumor bleeds easily. Metastasis and an elevated hCG level in a recently pregnant woman indicate choriocarcinoma. Metastasis and an elevated hCG level following an hydatidiform mole can either be choriocarcinoma or invasive mole. Since a biopsy is not usually done because of the risks, women with post-molar metastases are referred to as having metastatic trophoblastic disease (MTD) as a group.

Physical Examination

When GTD is suspected or diagnosed, the physical examination pays particular attention to the pelvis, abdomen (specifically the liver), the lungs and the brain.

Blood and Other Tests

- Complete blood count.
- Tests for liver enzymes and kidney function.
- Serum chemistries.
- Serum beta hCG.

Imaging

Studies in the evaluation of a hydatiform mole include:

- Pelvic ultrasound.
- Chest x-ray.

STAGING

NMTD is defined as having no disease outside the uterus and has a survival rate of 100 percent. Metastatic TD is further divided into low-risk (good prognosis) and high-risk (poor prognosis) based on several factors. Most physicians use the WHO (World Health Organization) scoring system of prognostic factors and not the FIGO staging system to determine which combination chemotherapy protocol to use. A total score of less than 8 is defined as low risk, 8-12 is medium risk and greater than 12 is high risk for treatment failure.

Table I

Prognostic Factor	Score
Age	
Less than 39	0
Greater than 39	1
Antecedent pregnancy	
Hydatidiform mole	0
Abortion	1
Term	2

Interval between end of antecedent pregnancy and start of chemotherapy

<4 months	0
4-6 months	1
7-12 months	2
>12 months	4

Table 1 (continued)

HCG (IU/mL)

<1,000	0
1,000-10,000	1
10,000-100,000	2
>100,000	4

ABO groups (female x male)

O x A or A x O	1
B or AB	2

Largest tumor, including uterine

3.5 cm	1
>5 cm	2

Site of metastases

Spleen, kidney	1
Gastrointestinal tract or liver	2
Brain	4

Number of metastases identified

1-4	1
4-8	2

TREATMENT OVERVIEW

Before starting chemotherapy for persistent NMTD, certain diagnostic tests should be performed including a chest x-ray and a computerized tomography (CT) scan of the abdomen, pelvis and head. Even when the chest x-ray is normal, a CT scan of the lungs may reveal small metastases in up to 40 percent of women. These women have a 50 percent failure rate with single drug chemotherapy. A complete blood count, platelet count and kidney and liver function tests are also required before initiating chemotherapy.

An important aspect of treating women with GTD is to start therapy as quickly as possible after the diagnosis is made. Chemotherapy is given until the serum hCG titer returns to normal.

Depending on the extent of the disease, most physicians give one to three cycles of chemotherapy following the first normal HCG level, then follow the titers monthly for 6 to 24 months after treatment. All women are advised to use oral contraceptives to prevent pregnancy for one to two years after therapy.

TREATMENT BY TYPE AND STAGE

HYDATIDIFORM MOLE (MOLAR PREGNANCY) (HM)

Complications associated with a molar pregnancy include anemia because of blood loss, severe high blood pressure, an overactive thyroid gland, heart failure, hemorrhage, infection and acute respiratory failure.

Standard Treatment As soon as the diagnosis is made, the HM is removed by a D&C in the operating room under anesthesia. For women who have completed childbearing, the removal of the uterus (hysterectomy) is also an option.

RH immune globulin is given to women with Rh negative blood to prevent Rh sensitization. In about one-third of women with a molar pregnancy, there may be enlargement of one or both ovaries because of multiple (theca-lutein) cysts caused by the high levels of hCG. Occasionally the cysts can rupture, bleed or become infected. In the vast majority of cases, these cysts do not have to be removed because they resolve with time, although sometimes it can take several weeks or months for them to disappear completely.

Chemotherapy may be given after the removal of the mole if the serum hCG rises for two successive weeks or plateaus for three weeks or more (in the vast majority of women with persistent GTD, the hCG level plateaus or rises by seven weeks after the D&C), if the serum hCG rises again after reaching a normal level, or if there is a hemorrhage not related to an incomplete D&C. These are cases presume to be NMTD. If metastases are

found it is called MTD. If choriocarcinoma is discovered in the microscopic examination of the tissue, it is then referred to as choriocarcinoma.

NON-METASTATIC GTD

Non-metastatic disease may be either an invasive mole or choriocarcinoma and is defined as having no disease outside the uterus.

Standard Treatment Chemotherapy for an invasive mole and non-metastatic choriocarcinoma is the same. All cases of non-metastatic GTD are considered curable, even if there is extensive local disease. If chemotherapy fails, a hysterectomy is usually performed.

The standard treatment is with a single chemotherapeutic drug. Most physicians use methotrexate if the liver tests are normal or actinomycin-D if they are not. There are several different ways methotrexate may be used. Methotrexate may be given daily, either by injection into a muscle or intravenously, for five days. This schedule is repeated every 14 days until the HCG level returns to normal. Three to four courses are usually required.

Methotrexate may also be given on days 1, 3, 5 and 7 with leucovorin given on days 2, 4, 6 and 8. When used in this fashion, only one course of treatment is given (with a cure rate of around 80 percent). A second or third course is given only if the HCG titer does not return to normal.

Methotrexate can be given by injection into a muscle every week until the hCG level is normal.

Methotrexate has also been given in very high amounts intravenously and also in pill form.

Actinomycin-D is usually given intravenously for five consecutive days and repeated every two weeks. Actinomycin-D can also be given in various doses on a single day and be repeated every two weeks or given if treatment with methotrexate fails to bring about normalization of the hCG level (titer remission).

Five-Year Survival 100 percent for both invasive mole and non-metastatic choriocarcinoma (NMTD).

LOW-RISK METASTATIC GTD

Metastatic choriocarcinoma is considered low-risk when it is diagnosed less than four months after the onset of the pregnancy, when the HCG titer is less than 40,000 mIU/mL, when there are no liver or brain metastases and when there has been no previous treatment with chemotherapy. A total WHO score less than 8 is also considered low risk

Standard Treatment Therapy for women with low-risk metastatic GTD is often with a single chemotherapeutic drug as for non-metastatic disease. But many physicians only

use single-agent chemotherapy for women who have an abnormal post molar HCG titer. All other cases with good prognostic features are treated with a combination of methotrexate + actinomycin-D with or without Cytosar (MAC or MA).

Those who fail chemotherapy with methotrexate alone (approximately 20 percent) are then treated with actinomycin-D or with MAC. MAC is given intravenously for five consecutive days every two to three weeks until the HCG titer returns to normal. Often one course is given after the hCG titer reaches normal.

Five-Year Survival 97 to 100 percent.

HIGH-RISK METASTATIC DISEASE

Metastatic choriocarcinoma is considered high-risk when it is diagnosed more than four months after the onset of pregnancy, associated with a serum HCG titer greater than 40,000 mIU/mL, liver or brain metastases, a history of chemotherapy or if it occurs after a full-term pregnancy, or if the WHO score is greater than 8.

Standard Treatment High-risk metastatic disease should be treated as soon as possible with aggressive chemotherapy. Women with brain or liver metastases are often treated with radiation therapy to the brain or liver.

Standard chemotherapy includes the drugs etoposide, methotrexate, actinomycin-D, vincristine and cyclophosphamide. Another regimen known as EMA-CE (cisplatin and etoposide are substituted for vincristine and cyclophosphamide) is also commonly used.

Five-Year Survival 75 percent.

TREATMENT FOLLOW-UP

A gynecologic examination and careful physical examination is done one week after the D&C for NMTD and then every four weeks until the hCG titer returns to normal or unless symptoms develop.

Regular measurements of the serum hCG levels are the most important part of the follow-up surveillance for GTD. The levels are monitored weekly until normal-usually, the level progressively declines to normal within 14 weeks after the D&C for NMTD. After normalization of the titers, the beta hCG is followed monthly for 6 to 12 months and for metastatic GTD every month for 2 to 3 years.

- Contraception (preferably oral contraceptives) should be used until pregnancy is permitted.

Pregnancy After GTD Treatment Most physicians recommend avoiding pregnancy for the first year after a hydatidiform mole is treated. This will prevent any confusion about the interpretation of elevated HCG levels.

Side effects from chemotherapy for GTD may affect future pregnancies. There may be a slightly higher infertility rate, a lower chance for a successful term pregnancy or a higher rate of spontaneous abortion. There does not appear to be an increased rate of birth defects in subsequent pregnancies. There is a higher incidence of subsequent GTD. An ultrasound, an hCG titer, and a chest x-ray are usually obtained in subsequent pregnancies to check for GTD.

RECURRENT GTD

Recurrence of disease occurs in 2.5 percent of women with non-metastatic disease, 3.7 percent of women with low-risk metastatic disease and 13 percent of women with high-risk metastatic disease. Almost all recurrences take place within 36 months of remission, with 85 percent before 18 months. Sometimes a recurrence can appear after an intervening normal pregnancy. Recurrent disease is usually treated with chemotherapy or occasionally surgery if the metastases are isolated. Cure rates vary, depending on the site of metastases.

THE MOST IMPORTANT QUESTIONS YOU CAN ASK

- What type of gestational trophoblastic disease do I have, and what is its extent?
- What is the likelihood of cure?
- How was the chemotherapy decided upon?
- What are my prospects of having a normal pregnancy later on?
- Will a specialist in gynecologic oncology be involved in my care?