



9195 Grant Street, Suite 410  
Thornton, CO 80229  
Phone: 303-280-2229(BABY)  
Fax: 303-280-0765

300 Exempla Circle, Suite 470  
Lafayette, CO 80026  
303-665-6016  
303-665-0121

6363 West 120<sup>th</sup> Avenue, Suite 300  
Broomfield, CO 80020  
303-460-7116  
303-460-8204

[www.whg-pc.com](http://www.whg-pc.com)

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## Gestational Trophoblastic Disease "GTD"

This is a term that includes several conditions that are associated with a complication of pregnancy. The conditions are molar pregnancy, invasive mole, metastatic mole and gestational choriocarcinoma. These are cancerous and precancerous conditions of the placenta. The concept is so far beyond most people's experience, that unless they have been to medical school they will never have heard of it. It is a surprisingly common condition!

### **How Does GTD Develop?**

The placenta is composed of three elements. The villi, the cytotrophoblast cells and the syncytiotrophoblast cells. The villi, (or villus when describing only one), is a microscopic finger-like structure containing a fetal blood vessel. It invades into the lining of the uterus. The syncytio- and cytotrophoblast cells surround the villi and help the villi to erode into the maternal blood vessels in the wall of the uterus.

The villi and the cyto- and syncytiotrophoblasts have to invade the lining of the uterus to reach the maternal blood vessels. As the pregnancy progresses the number of villi initially increases then begins to decrease as the placenta ages. At birth the placenta separates and along with the membranes and umbilical cord is discarded. They have done their job. This is the normal way the placenta functions. The invasion into the lining of the uterus is similar to the invasion of a cancer, but in pregnancy this is normal.

Sometimes something goes wrong very early in pregnancy. The fetus does not develop but the placental elements continue to grow. There is swelling of the villi and overgrowth of the cyto-and syncytiotrophoblasts cells. The villi can become so swollen that they are visible and look like drops of water. The scientific name for this mass of "water drops" is hydatidiform mole. (In Latin mole means shapeless mass and hydatid means water drop.) It is referred to as a mole or molar pregnancy. The trophoblastic cells make the pregnancy hormone, Human Chorionic Gonadotropin, HCG, which is the basis for all pregnancy tests. There is an overproduction of HCG as well as exaggerated symptoms of pregnancy.

Usually, the patient will spontaneously miscarry and pass the mole. If the molar pregnancy is detected before that happens then a D&C has to be done to evacuate the uterus. Obstetricians are well familiar with this condition and may be able to diagnose it by a sonogram. There is a characteristic appearance to the uterine contents, and there are no fetal structures or heart beat. Rarely there is a coexisting fetus, and sometimes the molar pregnancy is detected following is a normal delivery.

Why molar pregnancies occur is unknown, but there are some remarkable features about them:

- They have the ability to invade into the wall of the uterus.
- They can metastasize to other organs.
- They can develop into choriocarcinoma which is a virulent cancer. (rare)
- They have 23 pairs of chromosomes, all of which are paternal in origin.
- They are XX, and both of the X chromosomes are of paternal origin.
- The incidence in Asia is about 1 in 120 pregnancies.
- The incidence in Northern Europe is 1 in 2000 pregnancies.
- In the USA the incidence is about 1 in 1500 pregnancies.
- Metastatic disease sometimes undergoes spontaneous regression.

After the molar pregnancy is evacuated there must be rigorous surveillance for any sequelae. The consequences of a mole can be persistent mole, invasive mole, metastatic mole or choriocarcinoma. The follow up is done by a weekly blood test for a specific sub-unit of the HCG molecule called B-HCG (Beta HCG). The B-HCG has to fall to less than 2 to be normal. Usually the blood test is normal within 8 weeks. Then it is repeated every month for 6 months and then every

other month for 6 months. During this time the woman should not become pregnant again because that will also increase the B-HCG, and make things complicated. Therefore, the patient is placed on birth control for 6-12 months.

If the B-HCG decreases but then levels off and/or starts to rise again, then the diagnosis is Gestational Trophoblastic Disease. This may be either invasive mole (mole growing into the wall of the uterus), metastatic mole, (spreading usually to the lungs), or choriocarcinoma. At this point the patient is reexamined, a chest x-ray obtained and perhaps a scan of the liver. But for sure, the patient needs chemotherapy. If there is B-HCG, and the patient is not pregnant, she must be treated.

Treatment is usually easy. A single chemotherapeutic agent is given and repeated every two weeks until one course of treatment is given after the titer is normal (titer is the level of B-HCG in the blood). Then the patient is followed for a year with monthly B-HCG titers. As long as they remain normal everything is normal. After the year is up the patient can become pregnant again. The risk for another molar pregnancy is about doubled. But that is still a small number. If it were 1 in 1500 for the first mole it would be 1 in 750 for the next pregnancy.

Molar pregnancies and their management is the easy part. The problem is when they are ignored, not followed adequately, or inadequately treated, because then major problems occur. If a previous pregnancy ended in a miscarriage and there was no pathologic specimen it may have been an unknown molar pregnancy. If the last pregnancy was a normal term pregnancy and delivery, then nobody would be expecting choriocarcinoma to develop. But it can and it is usually not diagnosed promptly. It can be anywhere in the body and is a very aggressive cancer. It metastasizes widely and early. It is very invasive and destroys the tissue. It bleeds profusely. If it is in the brain then signs of a stroke or seizure may occur; if in the lung then the patient may cough up blood; if in the uterus then irregular bleeding. A simple pregnancy test that is positive will indicate the diagnosis.

Gestational trophoblastic disease is characterized as either metastatic or nonmetastatic. If nonmetastatic then treatment is by single agent chemotherapy or sometimes by hysterectomy. If metastatic, then it is divided into good prognosis and poor prognosis disease.

Poor prognostic disease indicates the need for more aggressive chemotherapy. This means a combination of drugs or the addition of surgery and or radiation to the treatment plan. The major concern is that it be treated aggressively.

|                      | <b>GOOD PROGNOSIS</b> | <b>POOR PROGNOSIS</b> |
|----------------------|-----------------------|-----------------------|
| Last pregnancy event | < 4 months            | > 4 months            |
| B-HCG level          | < 40,000              | > 40,000              |
| Prior pregnancy      | mole                  | term                  |
| Prior Treatment      | none                  | failed                |
| Metastases           | none or lung          | brain or liver        |

The high risk groups and the poor prognosis group requires aggressive multi-drug chemotherapy regimens. Resistant areas that can be irradiated are irradiated. Involved organs or parts of organs that can be removed are removed surgically. This is a cancer that can be cured, even when widely metastatic. The prognosis depends on the extent of disease and the aggressiveness of treatment. If a molar pregnancy is managed properly, the cure rate is about 100%. If non metastatic trophoblastic disease is vigorously treated the cure rate is also about 100%. Widely metastatic disease if recognized promptly and treated aggressively with multi-agent chemotherapy, surgery and radiation if necessary, is curable in about 80% of the cases.