



GESTATIONAL TROPHOBLASTIC DISEASE

This is a term that includes several conditions that are associated with the results of a pregnancy. The conditions are molar pregnancy, invasive mole, metastatic mole, and gestational choriocarcinoma (chorio carcinoma). These are cancers and cancer like conditions of placental elements. These conditions are very uncommon.

The easiest way to explain is to start at the beginning. In the beginning, a single egg produced by the mother is fertilized by a single sperm from the father. The egg and the sperm are unique because each has only one chromosome from each of the 23 pairs of chromosomes found in all other cells. At fertilization the complete complement of 23 pairs is thus restored. The fertilized egg divides and forms two daughter cells. Before division occurs it must duplicate its chromosomes so that each daughter cell has a complete complement of 23 pairs. This type of cell division is called mitosis. These two daughter cells divide by mitosis and so there are now four identical cells each with the normal 23 pairs of chromosomes. Further cell division results in 8, then 16, then 32, then 64 identical cells. Then things start to become complicated.

Certain cells begin to differentiate and become different from the other cells. Some of the cells will eventually form the extra-embryonic tissues, that is, the placenta, the membranes (bag of water), and the umbilical cord. The fetus is eventually formed by the remaining cells. The placenta is composed of three elements. The villi, the cytotrophoblast cells and the syncytiotrophoblast (sin sishio tro fo blast) 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.

There are millions of villi in a placenta. Oxygen and nutrients that are supplied to the fetus from the mother's blood must traverse the villus to be picked up by the fetal blood vessel in the villus. There is one fetal blood capillary per villus. The fetal blood is separate from the maternal blood. 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 syncytiotrophoblast 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.

Eventually, the patient will spontaneously miscarry and pass the mole. If the molar pregnancy is detected before that happens then an abortion has to be done to evacuate the uterus. Obstetricians are well familiar with this condition and can diagnose it by a sonogram. There is a characteristic appearance to the uterine contents, and there are no fetal structures or heartbeat. Only very rarely will there be a coexisting fetus.

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.
- They have 23 pairs of chromosomes, all of which are paternal in origin.
- They are XX, and both of the X chromosomes are also 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 hCG. Actually, it is for a specific sub-unit of the hCG molecule called B-hCG (Beta hCG). The B-hCG may be in the millions and has to fall to less than 2. 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.

If the B-hCG decreases but then levels off and 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, 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. This is one case where chemotherapy is given on the basis of a blood test without a tissue diagnosis. 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 2 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 may occur. 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.

High-risk groups and the poor prognosis groups require aggressive multi-drug regimens. Resistant areas that can be irradiated are irradiated. Involved organs or parts of organs that can be removed are removed surgically. The treatment is vigorous and at times ruthless. This is a cancer that can be cured, even though 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.

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