GESTATIONAL TROPHOBLASTIC DISEASE

Gtd, Pregnancy-Induced Cancer

A group of rare diseases in which abnormal trophoblast cells grow inside the uterus after conception.

Diagnosis  Female

About Gestational trophoblastic disease

Gestational trophoblastic disease (GTD) is a group of rare diseases in which a tumor develops inside the uterus from tissue that forms after conception (the joining of sperm and egg). This tissue (Pic. 1) is made of trophoblast cells and normally surrounds the fertilized egg in the uterus. Trophoblast cells help connect the fertilized egg to the wall of the uterus and form part of the placenta (the organ that passes nutrients from the mother to the fetus).

Sometimes there is a problem with the fertilized egg and trophoblast cells. Instead of a healthy fetus developing, a tumor forms. Until there are signs or symptoms of the tumor, the pregnancy will seem like a normal pregnancy.

Most GTD is benign (not cancer) and does not spread, but some types become malignant (cancer) and spread to nearby tissues or distant parts of the body.

GTD is a general term that includes different types of disease:

1. Hydatidiform moles (HM)
   - complete HM
   - partial HM
2. Gestational trophoblastic neoplasia (GTN)

- invasive moles
- choriocarcinomas
- placental-site trophoblastic tumors (PSTT; very rare)
- epithelioid trophoblastic tumors (ETT; even more rare)

**Hydatidiform mole (HM)**

Hydatidiform mole (Pic. 2, Pic. 3 and Pic. 4), also called molar pregnancy, is the most common type of GTD. Hydatidiform moles are slow-growing tumors that look like sacs of fluid. They are found in the uterus only and do not spread to other parts of the body. The cause of hydatidiform moles is not known.

Hydatidiform moles may be complete or partial:

- **Complete HM** forms when sperm fertilizes an egg that does not contain the mother's DNA (no nucleus). The egg has DNA from the father and the cells that were meant to become the placenta are abnormal.
- **Partial HM** forms when sperm fertilizes a normal egg and there are two sets of DNA from the father in the fertilized egg, so the embryo has 3 sets of chromosomes. Only part of the fetus forms and the cells that were meant to become the placenta are abnormal.

**Gestational trophoblastic neoplasia (GTN)**

Gestational trophoblastic neoplasia is a type of GTD that is almost always malignant and is generally treated by chemotherapy.

The following stages are used for gestational trophoblastic neoplasia:

- Stage I - the tumor is in the uterus only.
- Stage II - cancer has spread outside of the uterus to the ovary, fallopian tube, vagina, and/or the ligaments that support the uterus.
- Stage III - cancer has spread to the lung.
- Stage IV - cancer has spread to distant parts of the body other than the lungs.

Gestational trophoblastic neoplasia includes the following:

- **Invasive moles**

Invasive moles are made up of hydatidiforms that grow into the muscle layer of the uterus. Invasive moles are more likely to grow and spread than a hydatidiform.
mole. Rarely, a complete or partial hydatidiform mole may become an invasive mole. Sometimes an invasive mole will disappear without treatment.

- **Choriocarcinomas**

A choriocarcinoma is a malignant tumor that forms from persistent hydatidiform and spreads to the muscle layer of the uterus and nearby blood vessels. It can also grow from a bit of tissue left behind the uterus after miscarriage, an intended abortion or the delivery of a baby following an otherwise normal pregnancy. It may also spread to other parts of the body, such as the brain, lungs, liver, kidney, spleen, intestines, pelvis, or vagina.

- **Placental-site trophoblastic tumors**

A placental-site trophoblastic tumor (PSTT) is a rare type of gestational trophoblastic neoplasia that forms where the placenta attaches to the uterus. The tumor forms from trophoblast cells and spreads into the muscle of the uterus and into blood vessels. It may also spread to the lungs, pelvis, or lymph nodes. A PSTT grows very slowly and signs or symptoms may appear months or years after a normal pregnancy.

- **Epithelioid trophoblastic tumors**

An epithelioid trophoblastic tumor (ETT) is a very rare type of gestational trophoblastic neoplasia that may be benign or malignant. When the tumor is malignant, it may spread to the lungs.

In 2014, World Health Organization (WHO) modified prognostic scoring system of GTD stages (Pic . 5). In this scoring system, women with a score of 7 or greater are considered at high risk and score of <6 as low risk. Patients with low-risk disease usually receive less aggressive treatment than patients with high-risk disease.

Cases of GTD can be diagnosed through routine tests given during pregnancy, such as blood tests and ultrasound, or through tests done after miscarriage or abortion. Vaginal bleeding, enlarged uterus, pelvic pain or discomfort, and vomiting too much (hyperemesis) are the most common symptoms of GTD. But GTD also leads to elevated serum hCG (human chorionic gonadotropin hormone). Since pregnancy is by far the most common cause of elevated serum hCG, clinicians generally first suspect a pregnancy with a complication. However, in GTD, the beta subunit of hCG (beta hCG) is also always elevated. Therefore, if GTD is clinically suspected, serum beta hCG is also measured.
The initial clinical diagnosis of GTD should be confirmed histologically, which can be done after the evacuation of pregnancy in women with hydatidiform mole. However, malignant GTD is highly vascular. If malignant GTD is suspected clinically, biopsy is contraindicated, because biopsy may cause life-threatening bleeding.

Women with persistent abnormal vaginal bleeding after any pregnancy, and women developing acute respiratory or neurological symptoms after any pregnancy, should also undergo hCG testing, because these may be signs of a hitherto undiagnosed GTD.

In some very rare cases, a GTD can co-exist with a normal fetus. This is called a "twin pregnancy". These cases should be managed only by experienced clinics, after extensive consultation with the patient. Because successful term delivery might be possible, the pregnancy should be allowed to proceed if the mother wishes, following appropriate counseling. The probability of achieving a healthy baby is approximately 40%, but there is a risk of complications, e.g. pulmonary embolism and pre-eclampsia (a pregnancy complication characterized by high blood pressure). Compared with women who simply had a GTD in the past, there is no increased risk of developing persistent GTD after such a twin pregnancy.

After GTD treatment, it is still possible to become pregnant, even after chemotherapy treatment. Patients with chemotherapy need to wait a year after finishing the treatment before they try to get pregnant. Women with a hydatidiform mole have an excellent prognosis. Women with a malignant form of GTD usually have a very good prognosis.

After dilatation and curettage surgery, patients can usually try to get pregnant as soon as their hCG levels return to normal. The chance of having healthy baby is the same in women after GTD treatment as for any other woman of the same age.

After that, gestational trophoblastic disease doesn’t require or affect IVF outcome. Women after hysterectomy, removing the uterus, the only chance to have genetically related baby is through surrogacy (the carrying of a pregnancy for intended parents in third party uterus), if is permitted by local law.

**Associated diseases**

- menstrual cycle disorders
- amenorrhea
- ovarian cancer
- exaggerated placental site
- placental site nodule
- lung cancer

**Complications**
Uterus tumors of gestational trophoblastic disease cause the body to think it is pregnant. As an answer to high levels of hCG because of “pregnancy”, menstrual cycle is suspended. After surgery, hCG levels usually fall down to normal levels which induces resumption of menstrual cycle. The periods are stopped also during chemotherapy treatment. After that, chemotherapy treatment may cause early menopause, about 3 years earlier than usual.

When “twin pregnancy” occurs, it could be associated with complications such as pulmonary embolism and pre-eclampsia.

The term persistent trophoblastic disease (PTD) is used when after treatment of a molar pregnancy, some molar tissue is left behind and again starts growing into a tumor. Although PTD can spread within the body like a malignant cancer, the overall cure rate is nearly 100%. In the vast majority of patients, treatment of PTD consists of chemotherapy. Only about 10% of patients with PTD can be treated successfully with a second curettage.

In women who have a malignant form of GTD, hCG concentrations stay the same (plateau) or they rise. Persistent elevation of serum hCG levels after a non-molar pregnancy (i.e., normal pregnancy, or preterm pregnancy, or ectopic pregnancy (pregnancy taking place in the wrong place, usually in the fallopian tube), or abortion) always indicate persistent GTD (very frequently due to choriocarcinoma or placental site trophoblastic tumor), but this is not common, because treatment mostly is successful.

In rare cases, a previous GTD may be reactivated after a subsequent pregnancy, even after several years. Therefore, the hCG tests should be performed also after any subsequent pregnancy in all women who had had a previous GTD (6 and 10 weeks after the end of any subsequent pregnancy).

**Risk factors**

Most hydatidiform moles are benign, but they sometimes become cancer. Having one or more of the following risk factors increases the risk that a hydatidiform mole will become cancer:

- a pregnancy before 20 or after 35 years of age
- prior molar pregnancy
- prior miscarriage
- a very high level of beta human chorionic gonadotropin (β-hCG), a hormone made by the body during pregnancy
- a large tumor in the uterus
- an ovarian cyst larger than 6 centimeters
- high blood pressure during pregnancy
- hyperthyroidism (extra thyroid hormone is made)
- severe nausea and vomiting during pregnancy
- trophoblastic cells in the blood, which may block small blood vessels
- serious blood clotting problems caused by the hydatidiform mole
- beta-carotene deficiency
A choriocarcinoma is more likely to form in women who have had any of the following:

- pregnancy after 25 increases the risk until menopause
- molar pregnancy, especially with a complete hydatidiform mole
- normal pregnancy
- tubal pregnancy (the fertilized egg implants in the fallopian tube rather than the uterus)
- prior miscarriage

Other risk factors with very low risk of GTD:

- blood type (women with A or AB blood type are at slightly higher risk than those with B or 0 type)
- birth control pills
- family history (very rarely, molar pregnancies repeats in women of the same family)

Impact on fertility

Most women with GTD can become pregnant again and can have children again. The risk of a further molar pregnancy is low. More than 98% of women who become pregnant following a molar pregnancy will not have a further hydatidiform mole or be at increased risk of complications. The risk of a repeat GTD is approximately 1 in 100, compared with approximately 1 in 1000 risk in the general population. Especially women whose hCG levels remain significantly elevated are at risk of developing a repeat GTD.

Hysterectomy (surgical removal of the uterus) can also be offered to patients > 40 years of age or those for whom sterilization is not an obstacle. Only a few women with GTD have a poor prognosis, e.g. some forms of stage IV GTN.

Follow up is necessary in all women with gestational trophoblastic disease, because of the possibility of persistent disease, or because of the risk of developing malignant uterine invasion or malignant metastatic disease even after treatment in some women with certain risk factors.

The use of a reliable contraception method is very important during the entire follow up period, as patients are strongly advised against pregnancy at that time. If a reliable contraception method is not used during the follow-up, it could be initially unclear to clinicians as to whether a rising hCG level is caused by the patient becoming pregnant again, or by the continued presence of GTD.

Prevention
The best prevention for gestational trophoblastic disease is to avoid pregnancy. On the other hand, the disease is so rare, that its prevention isn’t suitable factor for family planning decisions, especially in women without GTD history.

**Symptoms**

These and other signs and symptoms may be caused by gestational trophoblastic disease or by other conditions:

- vaginal bleeding not related to menstruation
- an uterus that is larger than expected during pregnancy
- high blood level of hCG
- pain or pressure in the pelvis
- severe nausea and vomiting during pregnancy
- high blood pressure with headache and swelling of feet and hands early in the pregnancy
- vaginal bleeding that continues for longer than normal after delivery
- fatigue, shortness of breath, dizziness, and a fast or irregular heartbeat caused by anemia

GTD sometimes causes an overactive thyroid. Signs and symptoms of an overactive thyroid include the following:

- fast or irregular heartbeat
- shakiness
- sweating
- frequent bowel movements
- trouble sleeping
- feeling anxious or irritable
- weight loss

**Therapies**

**Self therapy**

Alternative therapy may be proposed as cancer cures. These treatments have not been proven safe and effective in clinical trials.

**Conventional medicine**
**Pharmacotherapy**

**Chemotherapy**

Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). Methotrexate and dactinomycin are among the chemotherapy drugs used in GTD.

The way the chemotherapy is given depends on the type and stage of the cancer being treated, or whether the tumor is low-risk or high-risk.

Chemotherapy with one or more anticancer drugs is used for treatment of low-risk gestational trophoblastic neoplasia (invasive mole or choriocarcinoma). Treatment is given until the $\beta$-hCG level is normal for at least 3 weeks after treatment ends.

If the level of $\beta$-hCG in the blood does not return to normal or the tumor spreads to distant parts of the body, chemotherapy regimens used for high-risk metastatic gestational trophoblastic neoplasia are given. Treatment of high-risk metastatic GTN (invasive mole or choriocarcinoma) may include the following:

1. combination chemotherapy (using more than one anticancer drug)
2. intrathecal chemotherapy and radiation therapy to the brain (for cancer that has spread to the lung, to keep it from spreading to the brain)
3. high-dose chemotherapy or intrathecal chemotherapy and/or radiation therapy to the brain (for cancer that has spread to the brain)

For disease that remains after surgery, treatment is usually chemotherapy. Even if the doctor removes all the cancer that can be seen at the time of the surgery, some patients may be given chemotherapy after surgery to kill any tumor cells that are left. This treatment (also called adjuvant therapy) is given to lower the risk that the cancer will come back after the surgery.

**Surgical therapy**

**Dilatation and curettage with suction evacuation (D&C)**
Dilatation and curettage with suction evacuation is a surgical procedure to remove abnormal tissue and parts of the inner lining of the uterus. Uterus should be larger than 16 weeks gravid size and ideally under ultrasound guidance. The cervix is dilated and the material inside the uterus is removed with a small vacuum-like device. The walls of the uterus are then gently scraped with a curette (spoon-shaped instrument) to remove any material that may remain in the uterus. This procedure may be used for hydatidiform mole.

After surgery, beta human chorionic gonadotropin (β-hCG) blood tests are done every week until the β-hCG level returns to normal. Patients also have follow-up doctor visits monthly for up to 6 months. If the level of β-hCG does not return to normal or increases, it may mean the hydatidiform mole was not completely removed and it has become cancer. Pregnancy causes β-hCG levels to increase, so your doctor will ask you not to become pregnant until follow-up is finished.

Hysterectomy

Hysterectomy is the surgery to remove the uterus, and sometimes the cervix and is a rarely indicated alternative if no further pregnancies are wished for by the female patient.

Other therapies

Radiotherapy

Radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy:

1. External radiation therapy uses a machine outside the body to send radiation toward the cancer.
2. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer.

The way the radiation therapy is given depends on the type of gestational trophoblastic disease being treated. External radiation therapy is used to treat gestational trophoblastic disease.

Radiotherapy can also be given to places where the cancer has spread, e.g. the brain.

Assisted reproduction
Assisted reproductive technology (ART) is the technology used to achieve pregnancy in procedures such as fertility medication, artificial insemination, in vitro fertilization and surrogacy. It is reproductive technology used primarily for infertility treatments, and is also known as fertility treatment. It mainly belongs to the field of reproductive endocrinology and infertility, and may also include intracytoplasmic sperm injection (ICSI) and cryopreservation. Some forms of ART are also used with regard to fertile couples for genetic reasons (preimplantation genetic diagnosis).

If conservative medical treatments fail to achieve a full term pregnancy, the physician may suggest the patient undergo in vitro fertilization (IVF). Infertile couples may also resort to egg donation or embryo donation when the female partner cannot have genetic children because her own eggs cannot generate a viable pregnancy. Surrogacy via a gestational carrier is also an option when a patient’s medical condition prevents a safe pregnancy, when a patient has ovaries but no uterus due to congenital absence or previous surgical removal, and where a patient has no ovaries and is also unable to carry a pregnancy to full term.

Among women with older reproductive age, with history of repetitive abortions or genetic disorders, genetic analysis is highly recommended. The PGS/PGD allows studying the DNA of eggs or embryos to select those that carry certain damaging characteristics. It is useful when there are previous chromosomal or genetic disorders in the family, within the context of in vitro fertilization programs.

The rate of success for IVF is correlated with a woman’s age. More than 40 percent of women under 35 succeed in giving birth following IVF, but the rate drops to a little over 10 percent in women over 40.

Find more about related issues

Therapies

Egg donation
Process by which a woman donates eggs for purposes of assisted reproduction or biomedical research.
Learn more at: www.fertilypedia.org/edu/therapies/egg-donation
ICSI
A micromanipulative fertilization technique in which a single sperm is injected directly into an egg.
Learn more at: www.fertilitypedia.org/edu/therapies/icsi

Sperm donation
The procedure in which a man (sperm donor) provides his sperm for fertility treatment.
Learn more at: www.fertilitypedia.org/edu/therapies/sperm-donation

Standard IVF
A process in which an egg is fertilised by sperm outside the body: in vitro. Own or donated gametes may be used.
Learn more at: www.fertilitypedia.org/edu/therapies/standard-ivf

Gallery

Pic. 4: Hydatidiform mole on CT, axial view
Pic. 3: Hydatidiform mole on CT, sagittal view
Pic. 1: Hydatidiform mole complete type
Histopathologic image of hydatidiform mole (complete type). Hematoxylin and eosin stain.

Pic. 2: Molar pregnancy
Transvaginal ultrasonography showing a molar pregnancy. The pattern is described as a bunch of grapes ("cluster of grapes" or "honeycombed uterus" or "snow-storm").

Pic. 5: Modified WHO Prognostic Scoring System

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