Gestational trophoblastic disease (GTD)

The term “gestational trophoblastic disease” (GTD) covers a cytogenetically and clinically heterogeneous group of clinical conditions characterized by disordered differentiation and/or the proliferation of trophoblastic epithelium. The morphological classification follows the WHO classification.

GTD - epidemiology

- The incidence is greater in women older than 40 years and younger than 20
- Risk factors: prior GTD
- Other risk factors: a diet low in vitamin A, low socioeconomic status and blood A group women married to group 0 men

Classification of gestational trophoblastic disease (GTD) according to clinical and pathobiological criteria based on the classification of the World Health Organization

Gestation trophoblastic disease GTD

- GTD is a heterogenous group of gestational and neoplastic conditions arising from trophoblast, including molar gestations and trophoblastic tumors.

Epidemiology

- The reported incidence of hydatidiform mole in developed countries is 1 per 591 pregnancies, with an incidence of GTD of 1 per 714 live births.
- The incidence of GTD increases with age and is correlated with ethnicity. The incidence for Asian women is double that reported for women of Caucasian descent.


GTD etiology

- Partial moles result from diandric triploidy
- Complete moles result from diandry (fertilization of an empty ovum) - 46 XX karyotype; the molar chromosomes are completely of paternal origin
- Up to 50% of choriocarcinomas follows complete moles

GTD – signs and symptoms

- Patients with partial molar gestations usually present as spontaneous abortion (sometimes with increased hCG levels)

Human chorionic gonadotropin hCG

- hCG, a 38-kDa glycoprotein hormone, is physiologically produced by syncytiotrophoblast cells in the placenta during pregnancy.
- It comprises two subunits (α and β polypeptide chains)
- Since the α-subunit of hCG has a sequence homology similar to other pituitary hormones, including luteinising hormone (LH), thyroid-stimulating hormone (TSH) and follicle-stimulating hormone (FSH), the β-subunit of hCG is assayed.
- Typically, serum β-hCG levels are markedly raised in germ cell tumours, particularly pure choriocarcinoma. Ectopic secretion of β-hCG by other non-germ cell neoplasms is rare.

GTD – signs and symptoms

A complete molar pregnancy usually presents with
- first trimester bleeding
- uterus larger than expected for gestational age
- the absence of fetal parts on ultrasound
- a markedly elevated beta-human chorionic gonadotropin (β-hCG)
Determination of Human Chorionic Gonadotropin (hCG)

- Apart from the histological proof of trophoblastic disease, determination of serum hCG levels is the most important aspect influencing the choice and duration of therapy; serum hCG is also used to assess the efficacy of treatment.
- In clinical practice, the hCG level may, in many cases, be the only tangible parameter indicating trophoblastic disease.

Clusters of vesicles can be seen macroscopically in a hydatidiform mole.
Nga Yin Cheung A Obst and Gyn. 2003, 17: 849-68

GTD

- Swollen villus and trophoblastic proliferation

GTD – signs and symptoms

- GTD should always be considered when a patient has continued vaginal bleeding following delivery or abortion!

Partial Mole

- Cytogenetically more than 90% of cases are triploid in origin (70% are 69XXY, 27% are 69XXX, 69XYY), two thirds of the genome are paternally derived and only one third from the mother.
- Partial moles are therefore also referred to as androgenetic in origin

Partial mole – clinical symptoms

- Clinical signs and symptoms such as abdominal pain, cramps of the lower abdomen and vaginal bleeding during pregnancy are non specific.
- The uterus is often large for gestational age, and fetal heart beat is usually absent.
Partial mole

• On ultrasound, findings include an enlarged placenta with grape-like clusters of villi.
• Serum hCG may be elevated.
• Embryonic or fetal development may be present but accompanied by malformations of varying severity. It is rare for a fetus to achieve viability.

Partial mole – ultrasound picture

Partial mole - treatment

• The goal of treatment for partial mole is the complete evacuation of trophoblastic material from the uterine cavity.
• Because of the risk of developing persistent GTD (0.5–2 %), regular weekly testing of serum hCG should be done after a partial mole has been diagnosed until the results for hCG are negative.

Complete mole

• Less commonly:

Complete mole

• Complete moles are characterised by the absence of a fetus or fetal parts (i.e. no embryonic tissues).
• There is a non-invasive, diffuse swelling of chorionic villi.
GTD – imaging; complete mole

- Scan of the uterus shows the classical bunch-of-grapes appearance or “snow-storm” appearance in the uterine cavity. This is the typical appearance of a complete mole.

Complete hydatidiform mole

- A mole involving most of the chorionic villi
- never contain fetal parts
- the chorionic epithelial cells are diploid - usually 46 XX kariotype; the molar chromosomes are completely of paternal origin
- For unknown reasons the incidence is higher in Asian countries than in Western hemisphere

<table>
<thead>
<tr>
<th>Complete mole</th>
<th>Partial mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>KARYOTYPE</td>
<td>46,XX; 46,XY</td>
</tr>
<tr>
<td>HGS</td>
<td>11111</td>
</tr>
<tr>
<td>UTERINE SIZE</td>
<td>1</td>
</tr>
<tr>
<td>CONCORD TO CHORIONICA</td>
<td>2%</td>
</tr>
<tr>
<td>FETAL PARTS</td>
<td>No</td>
</tr>
<tr>
<td>COMPONENTS</td>
<td>Expanded egg + single sperm (subsequently diploid paternal DNA); empty egg + 2 sperm is rare</td>
</tr>
<tr>
<td>RISK OF COMPLICATIONS</td>
<td>15–20% malignant trophoblastic disease</td>
</tr>
<tr>
<td>SYMPTOMS</td>
<td>Vaginal bleeding, enlarged uterus, hypertension, pre-eclampsia, hyperthyroidism</td>
</tr>
<tr>
<td>OUTCOME</td>
<td>Hydatidiform mole or “clusters of grapes” / “snowstorm” on ultrasound</td>
</tr>
</tbody>
</table>

Invasive complete mole

- a nonmalignant process characterized by penetration of the trophoblastic tissue into the myometrium and occasionally into the parametrium
- rarely metastasizes

Placental site trophoblastic tumor

- is a rare, slow growing form of GTD
- arise from intermediate trophoblasts at the placental implantation site, with late spread by local infiltration and via lymphatics.
Placental site trophoblastic tumor

- an infiltrating yellowish-white tumor with irregular contours that invades the whole thickness of the myometrium and projects into the endometrial cavity
- the tumor margin (yellow demarcation line)

Treatment

- In contrast to other trophoblastic tumors, PSTT is relatively insensitive to chemotherapy, and surgery is the primary therapeutic approach in patients presenting with disease limited to the uterus

Choriocarcinoma

- Choriocarcinoma is the most aggressive form of GTD with rapid growth and metastatic potential
- usually affects the placenta
- usually disseminates widely by the hematogenous route and is associated with distant metastases
- It is reported to commonly metastasize to the lungs and vagina and less commonly to the liver, brain, kidneys, and gastrointestinal tract, in that order.
- The disease can cross the placenta and metastasize within the fetus.

Choriocarcinoma

- Characteristic feature is the identification of intimately related syncytiotrophoblasts and cytotrophoblasts without formation of definite placental type villi

Choriocarcinoma

- The syncytiotrophoblasts are multinucleated and have a dark staining cytoplasm.
- The cytotrophoblasts are mononuclear and have a pale staining cytoplasm
Choriocarcinoma

- Choriocarcinoma of the placenta during pregnancy is preceded by:
  - hydatidiform mole (50% of cases)
  - spontaneous abortion (20% of cases)
  - ectopic pregnancy (2% of cases)
  - normal term pregnancy (20-30% of cases)

- It is also classified as a germ cell tumor and may arise in the testis or ovary.

Epithelioid trophoblastic tumor (ETT)

- ETT, the most recent addition to GTD, is an uncommon but unique proliferative lesion whose features mimic those of squamous-cell carcinoma (SCC)
- To date, less than 100 cases of ETT have been reported in the literature

ETT

- ETT is an unusual type of trophoblastic tumor with antecedent gestational events such as full-term deliveries, spontaneous abortions, and hydatidiform moles.
- The interval between the preceding gestation and the diagnosis of ETT ranges from 1 year to 18 years (average 6.2 years)
- Serum beta-human chorionic levels are nearly always elevated at the time diagnosis, although the levels are generally low (<2,500 mIU/ml) compared with those in patients with choriocarcinoma.
- Can occur in the uterine tissues as well as in the surrounding or distant organs. There are reports of ETT arising in the broad ligament and fallopian tube, paracervix, parametrium, periadnexal soft tissue, and ovary.
ETT - prognosis

- Metastasis and death occur in approximately 25% and 10% of patients, respectively.
- It is reported that ETT can metastasize to the lung as well as to the tissues such as brain, tonsil, and pelvic lymph node.

Case report

- A 21-year-old woman (G2, P1) is in the early second trimester. She has noted a small amount of vaginal bleeding for the past week. On physical examination the uterus measures large for dates. An ultrasound examination shows intrauterine contents with a “snowstorm appearance”, and no fetus is identified. The gross appearance of tissue obtained by dilation and curettage is shown:

Which of the following substances is most likely to be greatly increased in her serum?

- A acetylocholinesterase
- B alfa-fetoprotein
- C estradiol
- D human chorionic gonadotropin
- E human placental lactogen

A. acetylocholinesterase

- Neural tube defects can be distinguished from other fetal defects by use of the acetylocholinesterase test on amniotic fluid obtained by amniocentesis.
- If acetylocholinesterase and maternal serum alfa-fetoprotein are elevated, a neural tube defect is likely.
Amniocentesis is a prenatal test. During amniocentesis, an ultrasound transducer is used to show a baby’s position in the uterus. A sample of amniotic fluid is withdrawn for testing; usually carried out during weeks 15-20 of the pregnancy. The procedure is invasive and has a small associated risk of miscarriage, estimated to be about 1 in 100.

Neural tube defects

- Neural tube defects are birth defects of the brain, spine, or spinal cord. The two most common neural tube defects are spina bifida and anencephaly
- Folic acid prevents most neural tube defects.
- Foods with folic acid: leafy green vegetables, fruits, dried beans, peas, and nuts, enriched breads, cereals and other grain products

Folic acid

- Folic acid or folate is a B vitamin.
- It is also referred to as vitamin M, vitamin B\textsubscript{9}, vitamin B\textsubscript{12} (or folacin), pteroyl-L-glutamic acid, and pteroyl-L-glutamate
- Humans cannot synthesize folates \textit{de novo}; therefore, folic acid has to be supplied through the diet

B. alpha-fetoprotein

- A marker for some germ cell tumors that contain yolk sac elements
- Patients with hepatocellular carcinoma often have elevated serum alpha-fetoprotein concentrations

C. Estradiol

E. Human placental lactogen

- Estrogens can be elaborated by various ovarian stromal tumors, including thecomas and granulosa cell tumors (a decrease in maternal serum estriol suggests incipient abortion)
- Human placental lactogen is produced in small quantities in developing placenta, and serum levels typically are not measured

D. hCG

- The figure shows a hydatidiform mole (complete mole) with enlarged, grapelike villi that form the tumor mass in the endometrial cavity
- These trophoblastic tumors secrete hCG