



Pathology of Trophoblastic Diseases

Lecture 5

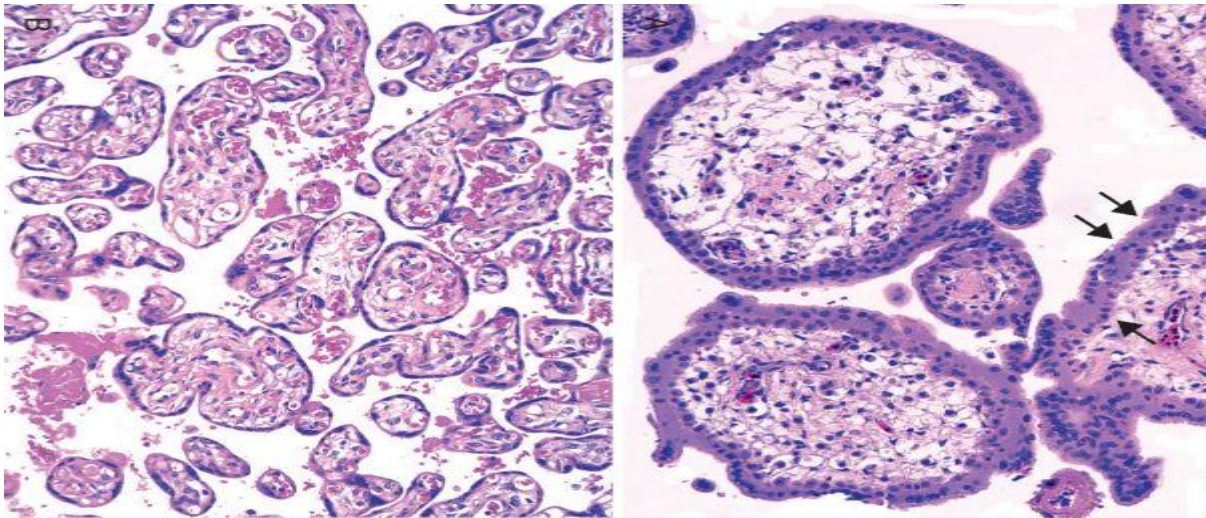
430 Pathology Team

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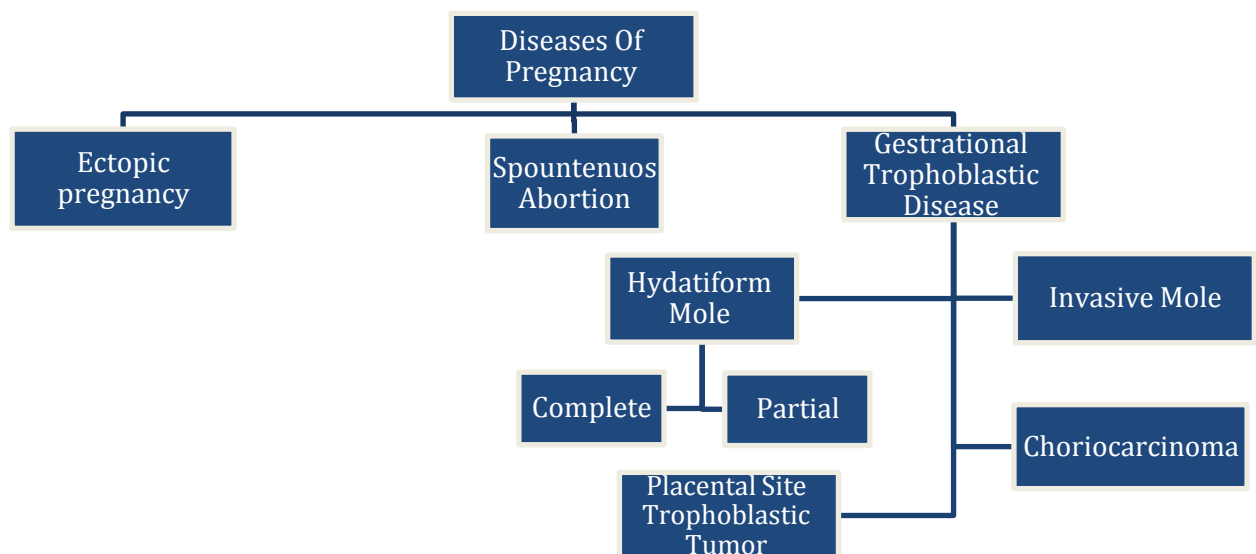
Red: Doctors' and important notes.
Green: Team notes.

Normal placenta:

The placenta is composed of chorionic villi that sprout from the chorion to provide a large contact area between the fetal and maternal circulations



Chorionic villi composed of delicate mesh of central stroma surrounded by two discrete layers of epithelium—the outer layer consisting of syncytiotrophoblast (*two arrows*) and the inner layer consisting of cytotrophoblast (*arrow*).



Ectopic Pregnancy:

Definition: it refers to the implantation of the developing blastocyst at any other site other than the endometrium (in other words, outside the uterine cavity).

Sites:

1. **Fallopian tubes:** (Over 95% of ectopic pregnancies) (tubal pregnancy).
 - Within the tube, up to 80% occur in the **ampulla**, 25% in the **isthmus**, 5% in the infundibulum and up to 2% in the interstitial portion.
 - **Right-sided ectopics are commoner than left-sided.**
2. Other sites include the **ovary, peritoneal cavity and uterine cervix.**

Etiology:

Pelvic inflammatory disease is the **most common** antecedent factor that can cause **adhesion**, inflammation, torsion and destruction of the fallopian tube.

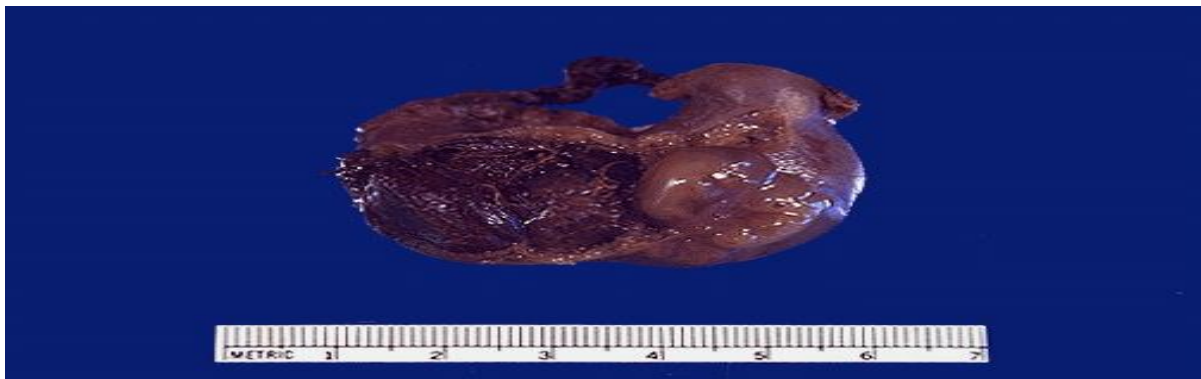
Other etiologic factors:

- Abnormal tubal motility or mucosal adhesions (that impede passage of the conceptus along the tube)
- Endometriosis
- Previous pelvic surgery.

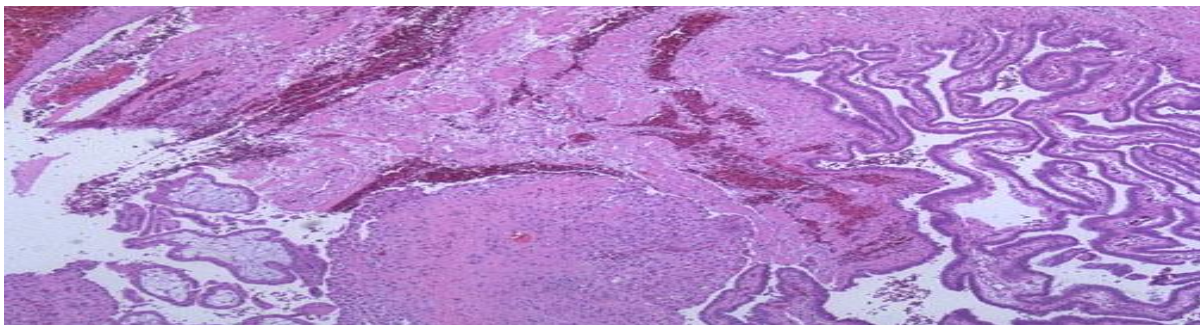
Clinical Features:

- **Not detected early** because the patient doesn't know that she is pregnant.
- **Pelvic pain or abnormal bleeding** following a period of **amenorrhoea**.
- The majority will present as an **emergency** case with **tubal rupture** because of the **enlargement of the fallopian tube** and hemorrhagic shock.

Microscopically: presence of villi lined by syncytiotrophoblast and cytotrophoblast from the placenta which is abnormally formed in the tube



This is a ruptured tubal ectopic pregnancy. Note the twin fetuses at the lower right adjacent to the blood clot at the left. About half of ectopic pregnancies occur because of an identifiable lesion such as chronic salpingitis from pelvic inflammatory disease or adhesions from appendicitis, endometriosis, or previous laparotomy. However, in half of cases no cause can be found.



A positive pregnancy test (presence of human chorionic gonadotropin), ultrasound, and culdocentesis with presence of blood are helpful in making the diagnosis of ectopic pregnancy. Seen here is tubal epithelium at the right, with rupture site and chorionic villi at the lower left.

Spontaneous abortion (SABs)/ Miscarriage:

Definition: spontaneous end of a pregnancy at a stage where the fetus is incapable of surviving

- Generally defined in humans before **20 weeks of gestation**
- It is the **most common complication** of early pregnancy and most common type of pregnancy loss.
- 10-25% of all clinically recognized pregnancies will end in miscarriage.
- Most **clinically apparent miscarriages occur during the first trimester**.

- Very early miscarriages—those that occur **before the sixth week LMP** (since the woman's Last Menstrual Period)—are medically termed **early pregnancy loss or chemical pregnancy**.
- Miscarriages that occur **after the sixth week LMP** are medically termed **clinical spontaneous abortion**

Causes:

- The cause of a miscarriage cannot always be determined.
- **Chromosomal abnormalities of the fetus are the most common cause of early miscarriages.**
- Miscarriages can occur for many reasons. Some of these causes include : Genetic, Uterine or Hormonal abnormalities like diabetes, collagen vascular disease (such as lupus), reproductive tract infections, Congenital (present at birth) abnormalities of the uterus

1. Chromosomal abnormalities:

- Half (50%) of the fetal tissue from 1st trimester miscarriages contain abnormal chromosomes. This number drops to 20% with 2nd trimester miscarriages.
- Chromosomal abnormalities also become more common **with aging, and women over age 35 have a higher rate of miscarriage than younger women (precious pregnancy)**
- Advancing maternal age is the most significant risk factor for early miscarriage in otherwise healthy women.
- **A pregnancy with a genetic problem has a 95% probability of ending in miscarriage.**

2. Hormonal problems :

- Cushing's Syndrome, thyroid disease, polycystic ovary syndrome**
- Diabetes** generally can be well managed during pregnancy.

If the diabetes is insufficiently controlled, it increases the risk of:

- miscarriages
- Baby can have major **birth defects**.

Therefore, good control of blood sugars during pregnancy is very important.

- Inadequate function of the corpus luteum in the ovary (which produces progesterone necessary for maintenance of the very early stages of pregnancy) leads **to progesterone deficiency which may lead to miscarriage. It is termed as "luteal phase defect"**

3. Infections:

- Listeria monocytogenes
- Toxoplasma gondii,
- Parvovirus B19,
- Rubella,
- Cytomegalovirus,
- Herpes simplex

Blood test (TORCH which is an abbreviation standing for different organisms: **T – Toxoplasmosis / Toxoplasma gondii, **O** – Other infections such as Parvovirus B19 , **R** – Rubella, **C** – Cytomegalovirus, **H** – Herpes simplex virus-2) is ordered by the clinician when a pregnant patient visits the clinic for the 1st time**

4. Maternal health problems such as Collagen vascular diseases:

Collagen vascular diseases are defined as diffuse immunologic and inflammatory changes in small blood vessels and connective tissue. Examples of collagen vascular diseases associated with an increased risk of miscarriage are **systemic lupus erythematosus**, and **antiphospholipid antibody syndrome**.

5. Lifestyle (i.e. smoking, drug use, malnutrition, excessive caffeine and exposure to radiation or toxic substances)

6. Abnormal structural anatomy of the uterus :

In some women there can be a tissue bridge (uterine septum), that acts like a partial wall dividing the uterine cavity into sections. The septum is not well suited for placental attachment and growth. Therefore, an embryo implanting on the septum would be at increased risk of miscarriage.

Fibroids can uncommonly **interfere with the embryo implantation** and the embryo's blood supply, thereby causing miscarriage

7. Maternal age: SABs increase after age 35 due to ovum abnormalities

8. Maternal trauma

9. Invasive surgical procedures in the uterus, such as amniocentesis and chorionic villus sampling **that are used in detecting genetic diseases of the fetus such as Down syndrome**, also slightly increase the risk of miscarriage

Diagnosis:

A miscarriage can be confirmed by:

1. **ultrasound (empty sac)**
2. Genetic tests may also be performed to look for abnormal chromosome arrangements **(to see if the fetus was aborted due to chromosomal abnormality. if so then next pregnancy should be monitored)**
3. Examination of the passed tissue **(confirmation of the diagnosis should be done by histopathological examination of the tissue).**

Microscopic examination of the products of conception:

It shows the presence of chorionic Villi (fetal tissue) in a sac of hemorrhagic tissue, trophoblast, fetal parts, and background gestational changes in the endometrium.

Gestational Trophoblastic Disease (GTD):

Definition: disease constitutes a spectrum of tumors and tumor-like conditions characterized by **proliferation of placental tissue**, either villous or trophoblastic.

Types: (GTD) can be benign or malignant. Majority of GTD cases are noncancerous (benign).

Prognosis: most forms of gestational trophoblastic disease can be cured with prompt management and most women who have had gestational trophoblastic disease can have normal pregnancies later

Treatment: surgery and chemotherapy are the most common forms.

Diagnosis:

- **Clinical symptoms and the imaging studies.**
- A blood test for the human chorionic gonadotropin (HCG) hormone is most commonly used to **diagnose and follow up** GTD.
- Serum HCG is markedly increased in GTD.
- Serum HCG is also elevated in normal and ectopic pregnancy, choriocarcinoma and germ cell tumor.
- Serum HCG levels continue to rise after 14th week as opposed to drop in normal gestation

Histologically:

It is classified into:

1. Hydatidiform mole (complete and incomplete)
2. Invasive mole **to the uterus** (chorioadenoma destruens)
3. Choriocarcinoma
4. Placental site trophoblastic tumor (PSTT).

1. Hydatidiform Mole (HM):

Histologically: is characterized by cystic swelling of the chorionic villi (trophoblast) and edematous changes is seen in all the types, accompanied by variable trophoblastic proliferation. This will lead to enlargement that will fill up and extend the cavity of the uterus in some cases especially with the complete type.

Grossly: looks like a bunch of grapes after abortion.

Symptoms:

- Patients present with increased abdominal swelling (rapid increase in uterine size) mistaken for normal pregnancy but the uterus is disproportionately large for stage of pregnancy.
- In addition patient has some vaginal bleeding, severe nausea and vomiting (because of the elevated level of hCG).

Cause: abnormal gametogenesis and fertilization.

Types:

- A. Complete HM
- B. Partial HM

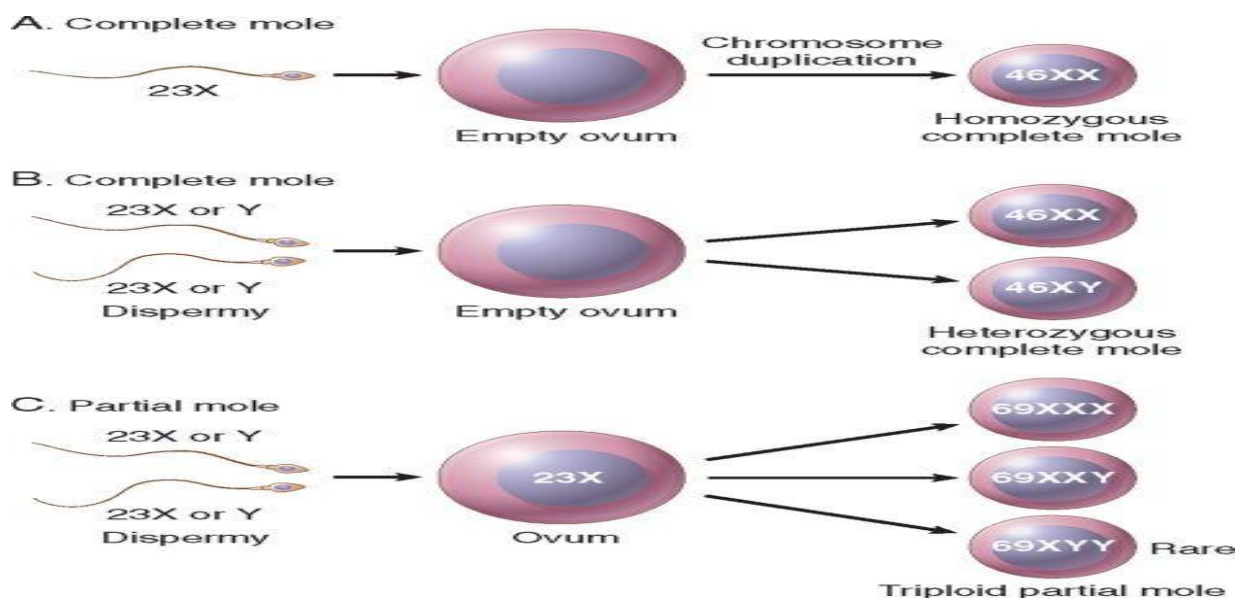
A. Complete HM:

Definition: genetically abnormal placenta with hyperplastic trophoblast, without fetus or embryo (main difference between complete and partial moles).

Morphology: uterus is distended and filled with swollen/large villi. No embryo, or fetal tissue is present.

Characteristics:

- There is elevated HCG levels.
- On chromosomal analysis there are (diploid) 46 chromosomes (2 haploid sets), 46XX karyotype and all the chromosomes come from the male (paternal side).



Treatment: evacuation of uterus by curettage, chemotherapy.

Prognosis:

- with appropriate therapy cure rate is very high
- spontaneous regression in 81%
- 17% developed an invasive mole (invading the myometrium layer)
- 2% developed choriocarcinoma

B. Partial Mole (PM):

Definition: genetically abnormal placenta with a mixture of large and small villi with slight hyperplasia of the trophoblast, filling the uterus. **Embryonal/fetal tissue is present.**

Grossly large vesicular chorionic villi mixed with normal-appearing villi.

Characteristics:

- It makes up 15–35% of all moles
- **Uterine size usually small or appropriate for gestational age**
- Serum hCG levels elevated but not as high as complete mole.
- Chromosomal analysis of partial moles **shows 69 chromosomes** (i.e. 3 haploid sets also called as triploidy), XXY in which **2 haploids are paternal (from the male) and one is maternal**

Prognosis:

Risk for development of choriocarcinoma **is very low**. Only 2-3% becomes malignant. Follow-up is mandatory.

2. Invasive Mole:

Definition: hydatidiform mole, generally of the **complete type**, in which villi **penetrate deeply in the myometrium and/or its blood vessels**.

Characteristics:

- It occurs in about 15% of complete moles and rarely in partial mole.
- Can cause hemorrhage and uterine perforation **(if it invades the full thickness of the wall)**.

3. Choriocarcinoma:

Definition: **malignant tumor** derived from normal or abnormal placental tissue, composed of a proliferation of **malignant cytotrophoblast and syncytiotrophoblast**, **without villi formation**.

Characteristics:

- It is an **aggressive malignant neoplasm** (necrosis, invasion, destruction, hemorrhage). However, it **responds well to chemotherapy**
- It is characterized by **highly increased serum concentration of HCG**.
- Choriocarcinomas are **aneuploid**.
- **It spreads early via blood to the lungs and other organs**.
- **About half** the choriocarcinoma are preceded by **complete hydatidiform mole**.
- Others are preceded by partial mole (very unusual), abortion, ectopic pregnancy and occasionally **normal term pregnancy**.

Summary

- **Ectopic Pregnancy:** implantation of the developing blastocyst at any other site other than the endometrium (in other words, outside the uterine cavity). Most commonly in Fallopian tubes (tubal pregnancy) up to 80% occur in the ampulla. **Most common cause is Pelvic inflammatory disease.** **Clinical Features:** the majority will present as an emergency case with tubal rupture and hemorrhagic shock. **Microscopically:** presence of villi lined by syncytiotrophoblast and cytotrophoblast from the placenta which is abnormally formed the tube
- **Spontaneous abortion:** end of a pregnancy at a stage where the fetus is incapable of surviving. It is generally defined in humans before 20 weeks of gestation. Very early miscarriages—those that occur before the sixth week LMP early pregnancy loss or chemical pregnancy while miscarriages that occur after the sixth week LMP are clinical spontaneous abortion. Chromosomal abnormalities of the fetus are the most common cause of early miscarriages. it can occur for many reasons. Some of these causes include: Genetic, Uterine or Hormonal abnormalities like diabetes, collagen vascular disease (such as lupus), reproductive tract infections, and Congenital (present at birth) abnormalities of the uterus. **Diagnosis:** can be confirmed by: ultrasound, genetic tests, examination of the passed tissue which shows the presence of chorionic Villi (fetal tissue) in a sac of hemorrhagic tissue, trophoblast, fetal parts, and background gestational changes in the endometrium.
- **Gestational Trophoblastic Disease (GTD):** characterized by proliferation of placental tissue, either villous or trophoblastic. Majority of GTD cases are noncancerous (benign). A blood test for the human chorionic gonadotropin (HCG) hormone is most commonly used to diagnose and follow up GTD. Serum HCG levels continue to rise after 14th week as opposed to drop in normal gestation
- **Histologically:** It is classified into: Hydatidiform mole (complete and incomplete), Invasive mole (chorioadenoma destruens), Choriocarcinoma, Placental site trophoblastic tumor (PSTT).
Hydatidiform Mole (HM): is characterized by cystic swelling of the chorionic villi (trophoblast) looks like a bunch of grapes after abortion. **Symptoms:** patients present with increased abdominal swelling mistaken for normal pregnancy but the uterus is disproportionately large for stage of pregnancy. **Cause:** abnormal gametogenesis and fertilization. **Types:** Complete and Partial
- **Complete HM:** abnormal placenta with hyperplastic trophoblast, without fetus or embryo. **Characteristics:** on chromosomal analysis there are (diploid) 46 chromosomes, 46XX karyotype and all the chromosomes come from the male (paternal side).
- **Partial Mole (PM):** abnormal placenta with a mixture of large and small villi with slight hyperplasia of the trophoblast, filling the uterus. Embryonal/fetal tissue is present. **Characteristics:** uterine size usually small or appropriate for gestational age, Serum hCG levels elevated but not as high as complete mole, Chromosomal analysis of partial moles shows 69 chromosomes XXY in which 2 haploids are paternal (from the male) and one is maternal
- **Invasive Mole:** complete type, in which villi penetrate deeply in the myometrium and/or its blood vessels.
- **Choriocarcinoma:** proliferation of malignant cytotrophoblast and syncytiotrophoblast, without villi formation. **Characteristics:** It is an aggressive malignant neoplasm (necrosis, invasion, destruction, hemorrhage). However, it responds well to chemotherapy, it is characterized by highly increased serum concentration of HCG, they are aneuploid. It spreads early via blood to the lungs and other organs.

Questions

1. A 22-year-old woman passes grape-like masses of tissue per vagina in the 16th week of her first pregnancy. She had not felt any fetal movement at any time. On physical examination she measures 18 weeks in size. A D&C is performed, yielding 1000 cc of 0.5 to 1.5 cm fluid-filled vesicles. Microscopic examination of this tissue shows large avascular villi along with trophoblastic proliferation. Which of the following is the best method to employ for her follow-up care?

- A. Chest radiograph
- B. Serum beta-HCG
- C. Endometrial biopsy
- D. Pelvic ultrasound
- E. Pap smear

Answer: (B). She has a hydatidiform mole. Persistence or an increase in the HCG level should suggest that trophoblastic disease is still present, such as invasive mole or choriocarcinoma.

2. A 32-year-old G3 P2 woman goes for a routine prenatal check at 12 weeks. On physical examination she is found to be large for dates, and no fetal heart tones are audible. An ultrasound is performed and revealed that no fetus was present, only many echogenic cystic areas within the uterus. Which of the following is the most likely diagnosis?

- A. Invasive mole
- B. Partial hydatidiform mole
- C. Placental site trophoblastic tumor
- D. Choriocarcinoma
- E. Complete hydatidiform mole

Answer: (E). No fetus is present, only grape-like chorionic villi that produce the echogenic effect on ultrasound. Complete mole is the most common form of gestational trophoblastic disease.

3. a 36 year old gravid female notes vaginal bleeding. Ultrasound reveals small grape-like cystic structures without evidence of a developing embryo. A diagnosis of complete hydatidiform mole is made at the hospital. Further analysis is most likely to reveal that:

- A. hCG levels are markedly decreased
- B. serum levels of alpha fetoprotein are elevated
- C. the genotype of the mole is 46,XX and is completely paternal in origin
- D. the genotype of the mole is triploid
- E. two or more sperm fertilized the ovum

Answer: (C). A complete hydatidiform mole is characterized by elevated hCG and grape like cystic structures filling the uterus with no detectable embryo on ultrasound. The genotype of a complete hydatidiform mole is purely paternal, caused by fertilization of an egg that has lost its chromosomes. Hydatidiform mole is associated with increasing maternal age, and may be a precursor to choriocarcinoma.