

Reproductive

Team *of* Pathology

Hazim
Jokhadar

Rawan
Al hyyan

Majed
Al shemari

Noura
Al refae

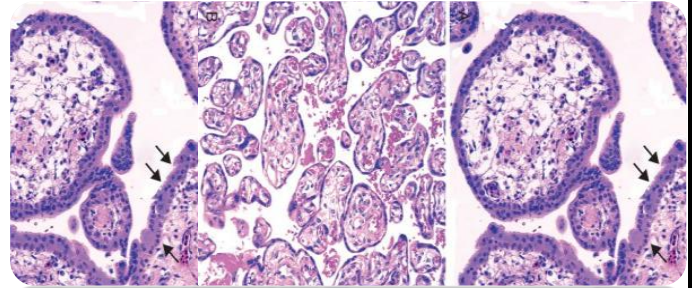
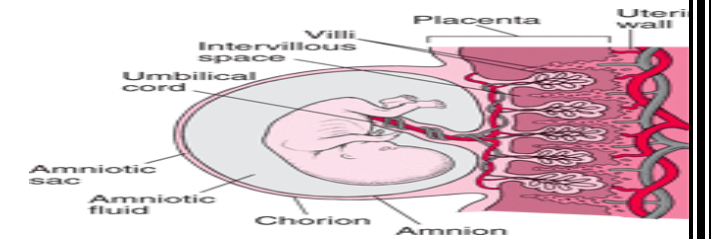
Pathology of trophoblastic disease



5th Lecture

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:** Ectopic pregnancy refers to the implantation of the **developing blastocyst** at any other site **other than the endometrium**.
- **Sites:**
 - **Fallopian tubes:** (**Over 95%** of ectopic pregnancies).
 - 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.
 - **Other sites** include the **ovary**, **peritoneal cavity** and **uterine cervix**.
- **Etiology:**
 - **Pelvic inflammatory disease** is the most common antecedent factor.
 - Other etiologic factors:
 - **Abnormal tubal motility or mucosal adhesions** (that impede passage of the conceptus along the tube)
 - **Endometriosis**
 - Previous pelvic surgery.

Ectopic means the displacement or the occurrence of something away from its normal position.

Clinical Features:

- **Pelvic pain** or **abnormal bleeding** following a period of amenorrhoea.

- The majority will present as an **emergency with tubal rupture** (when there is rupture of one tube it should be removed and the patient can use the other fallopian tube later on life) and **hemorrhagic shock**.

In early ectopic pregnancy the symptoms are often like a normal pregnancy such as amenorrhoea .

Then the first signs of an ectopic pregnancy appear (including pelvic pain and abnormal bleeding)

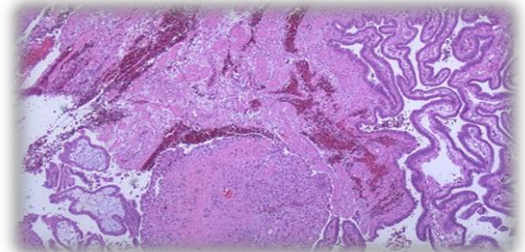
As the ectopic pregnancy progresses these symptoms worsen and other symptoms develop (including tubal rupture and hemorrhagic shock)

It can be diagnosed by \uparrow HCG (which also \uparrow in a normal pregnancy) and by radiology using ultrasonography.

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**(is a surgical procedure involving a large **incision through the abdominal wall to gain access into the abdominal cavity**). However, in **half** of cases **no cause can be found**.

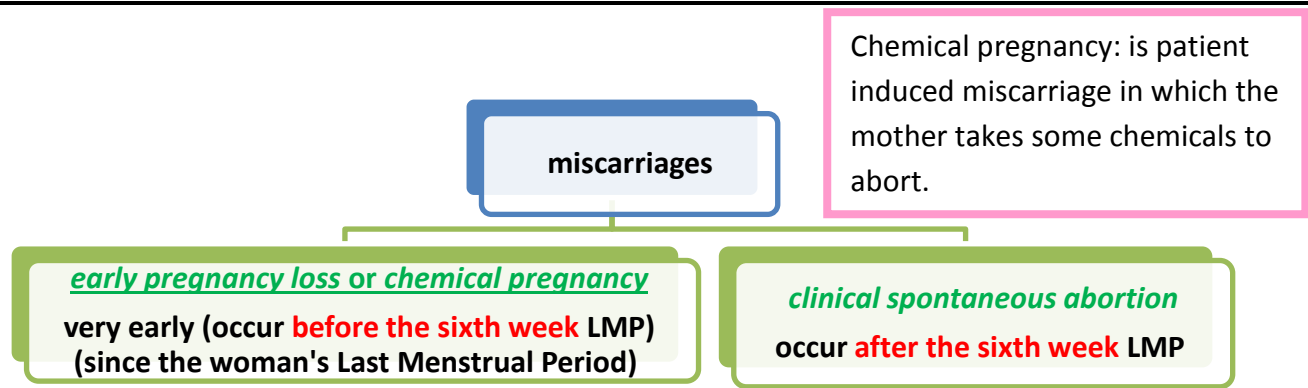


Seen here is tubal epithelium at the right, with rupture site and **chorionic villi** at the lower left.



Spontaneous abortion / Miscarriage:

- 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.



Causes of Spontaneous abortion/miscarriage:

The cause of a miscarriage cannot always be determined.

- 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
- Most clinically apparent miscarriages occur **during the first trimester**.
- **Chromosomal abnormalities of the fetus are the most common cause of early miscarriages.**

1.Chromosomal abnormalities: (the leading cause)

- 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
- 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 :

A. Cushing's Syndrome, thyroid disease, polycystic ovary syndrome

B. Diabetes generally can be well managed during pregnancy.

- If the diabetes is insufficiently controlled, risk of
 - ❖ miscarriages
 - ❖ baby can have major **birth defects**.

Good control of blood sugars during pregnancy is very important.

C. Inadequate function of the corpus luteum in the ovary (which produced 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: (TORCH infection)

- *Listeria monocytogenes*,
- *T-Toxoplasma gondii*,
- **Parvovirus B19**,
- **R** -Rubella,
- **C** -Cytomegalovirus,
- **H** -Herpes simplex

○-Others : Parvovirus B19, *Listeria monocytogenes*

4. Maternal health problems

Collagen vascular diseases:

Examples of collagen vascular diseases associated with an increased risk of miscarriage are **systemic**

*Collagen vascular diseases are illnesses in which a person's own immune system attacks their own organs.

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: Spontaneous abortions increase after age 35 due to ovum abnormalities

8. Maternal trauma

9. Invasive surgical procedures in the uterus, such as **amniocentesis**(amniotic fluid test in which a small amount of amniotic fluid taken by insertion of the needle used to withdraw the fluid) **and chorionic villus sampling**, also slightly increase the risk of miscarriage

Spontaneous abortion / Miscarriage: Diagnosis:

- A miscarriage can be confirmed by
- ❖ **Ultrasound** and
- ❖ **Examination** of the passed tissue.

Microscopic examination of the products of conception: Villi, trophoblast, fetal parts, and background gestational changes in the **endometrium**.

- Genetic tests may also be performed to look for abnormal **chromosome arrangements**.

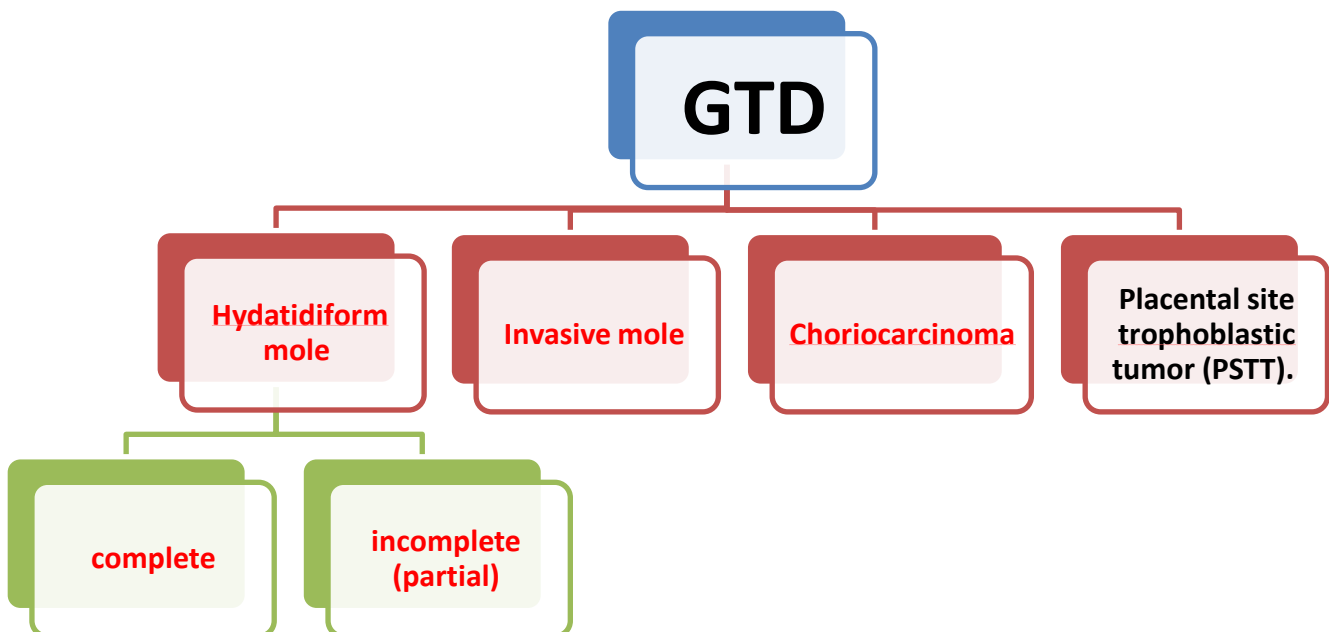
Gestational Trophoblastic Disease:

- Gestational trophoblastic disease constitutes a spectrum of **tumors and tumor-like** conditions **characterized by** proliferation of placental tissue, either **villous** or **trophoblastic**.
- Gestational trophoblastic disease (GTD) can be **benign** or **malignant**.
- **Majority** of GTD cases are **noncancerous**.
- Most forms of gestational trophoblastic disease **can be cured** with prompt management.
- **Surgery and chemotherapy** are the most common forms of treatment.
- Most women who have had gestational trophoblastic disease can have normal pregnancies later.

Diagnosis:

- A blood test for the human chorionic gonadotropin (HCG) hormone is **most commonly** used to diagnose **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:



Hydatidiform Mole:

- Hydatidiform mole is characterized histologically by cystic swelling of the chorionic villi, accompanied by variable **trophoblastic proliferation** (in both layers).
- Grossly it looks like a bunch of **grapes**.

*Hydatidiform: cyst filled with fluid.

*mole: abnormal pregnancy.

HM: enlarged edematous chorionic villi filling the uterus cavity. **Histologically** enlarged edematous chorionic villi filling the uterus cavity with hyperplasia

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 vomiting** (more than normal that would be expected).

It begins with amenorrhea (like a normal pregnancy) for 1 month but then the uterus enlarges much more rapidly than in a normal pregnancy for 3 months.

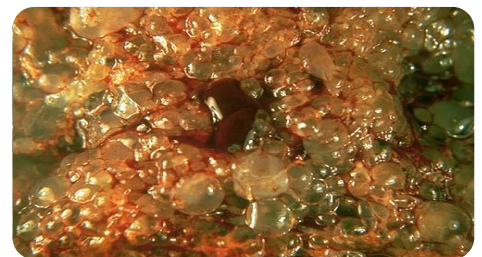
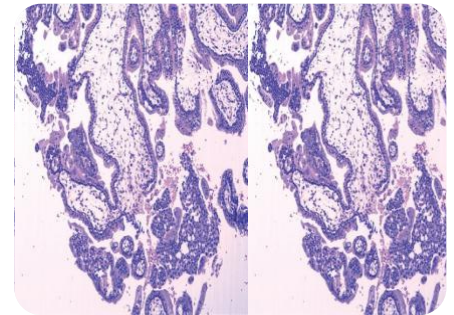
Caused by abnormal gametogenesis and fertilization.

There are 2 types of hydatidiform mole (HM): **Complete HM** and **Partial HM**.

Complete HM:

Chorionic villi are abnormal

- ▶ Definition: Genetically abnormal placenta with hyperplastic trophoblast, **without fetus or embryo**.
- ▶ Uterus is distended and filled with **swollen**/large villi. **No embryo**, or fetal tissue is present.
- ▶ There is **elevated HCG levels**
- ▶ On chromosomal analysis there are 46 chromosomes (2 haploid sets or diploidy), **46XX karyotype** and **all the chromosomes come from the male/paternal side**.
- ▶ **(exceeding those produced by a normal pregnancy of similar age)**
- ▶ Treatment : **Evacuation** of uterus by curettage(to remove tissue by scraping). **chemotherapy**(rarely).
- ▶ With appropriate therapy **cure rate is very high**:
 - ▶ **spontaneous regression** in 81%
 - ▶ 17% developed an **invasive mole**(invade myometrium so we remove the whole uterus)
 - ▶ 2% developed **choriocarcinoma**



Gray-like edematous villi that are filling the uterus cavity

Partial Mole (PM):

Normal chorionic villi

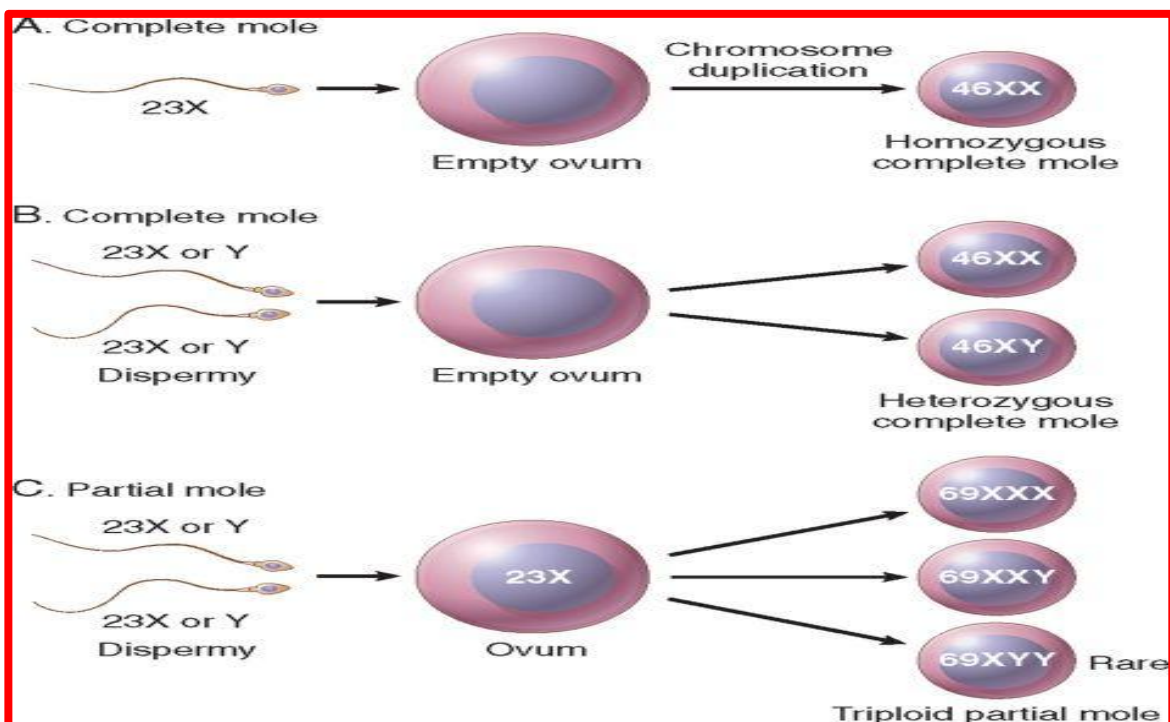
- ▶ **Definition:** genetically abnormal placenta with a mixture of **large and small villi** with **slight hyperplasia** of the trophoblast, filling the uterus.

- ▶ Embryonal/fetal tissue **is present**.
- ▶ **Grossly large vesicular** chorionic villi **mixed with normal**-appearing villi.
- ▶ 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 **very low**. Only 2-3% become malignant. Follow-up is mandatory.

Complete mole VS partial mole

feature	Complete mole	Partial mole
karyotype	46 XX (46,XY) haploid or diploid	Triploid (69)
chromosomes	No maternal (all paternal)	There is maternal but little
Fetal parts	No embryo or fetal tissue present	present
Villous edema	All villi	Some villi
HCG levels	elevated	Less elevated
Behavior	2% choriocarcinoma (also it can lead to invasive mole)	Rare choriocarcinoma

Empty ovum: ovum without nucleus because of genetic



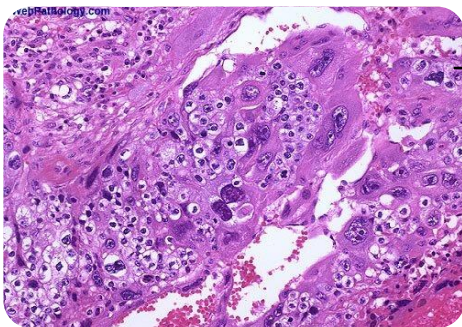
It can invade the myometrium to the inner third or even penetrate the uterus

Invasive Mole:

- ▶ **Definition:** Hydatidiform mole, generally of the **complete type**, in which **villi penetrate deeply in the myometrium** and/or its **blood vessels**.
- ▶ It occurs in about **15% of complete moles** and rarely in partial mole.
- ▶ Can cause **hemorrhage** and **uterine perforation**.

Choriocarcinoma: (germ cell tumor) (only trophoplast no villi)

- ▶ **Definition:** **Malignant** tumor derived from normal or abnormal placental tissue, composed of a **proliferation of malignant cytotrophoblast and syncytiotrophoblast, without villi formation**.
- ▶ It is an **aggressive malignant** neoplasm. (like to metastasize)
- ▶ It is characterized by **highly increased** serum concentration of HCG. (more than in HM)
- ▶ Choriocarcinomas are **aneuploid** (abnormal chromosomes number)
- ▶ It spreads early via **blood to the lungs and other organs**.
- ▶ Responds well to **chemotherapy**
- ▶ **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**.



▶ This image shows admixture of polygonal cells with clear cytoplasm (**cytotrophoblast**) large multinucleated cells with smudged nuclear chromatin (**syncytiotrophoblast**).



SUMMARY

Robbins

Gestational Trophoblastic Disease

Molar disease is due to an abnormal contribution of paternal chromosomes in the gestation. Partial moles are triploid and have two sets of paternal chromosomes. They are typically accompanied by a triploid embryo or fetus. There is a low rate of persistent disease. Complete moles are diploid or near diploid, and all chromosomes are paternal. No embryonic or fetal tissues are associated with complete mole. Among complete moles, 10% to 15% have persistent disease, usually invasive mole. Only 2% of complete moles subsequently develop choriocarcinoma. Gestational choriocarcinoma is a highly invasive and frequently metastatic tumor that, in contrast to ovarian choriocarcinoma, is highly responsive to chemotherapy and curable in most cases. Placental site trophoblastic tumor is an indolent and usually early-stage tumor of intermediate trophoblast that produces human placental lactogen and does not respond well to chemotherapy.

Robbins

Table 19-3. Features of Complete and Partial Hydatidiform Mole

Feature	Complete Mole	Partial Mole
Karyotype	46,XX (46,XY)	Triploid (69,XXY)
Villous edema	All villi	Some villi
Trophoblast proliferation	Diffuse; circumferential	Focal; slight
Atypia	Often present	Absent
Serum hCG	Elevated	Less elevated
hCG in tissue	++++	+
Behavior	2% choriocarcinoma	Rare choriocarcinoma

hCG, human chorionic gonadotropin.

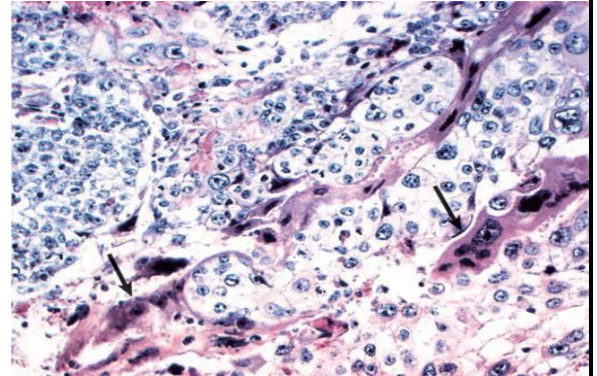
1- A 20-year-old woman presents to her gynecologist with a 3-day history of vaginal bleeding. An ultrasound shows a dilated endometrial cavity. Evacuation of the uterus by suction curettage reveals grapelike clusters and fetal parts. Cytogenetic examination of this tissue will most likely demonstrate which of the following genetic patterns?

- (A) Aneuploidy
- (B) Diploidy
- (C) Euploidy
- (D) Haploidy
- (E) Triploidy

2- A 41-year-old immigrant woman from Asia presents for prenatal care. Her uterus is significantly larger than expected, and her serum hCG level is much higher than expected for her due date. No fetus is found on ultrasound examination. The abnormal placenta is removed. One month later, this patient presents to the emergency room with abdominal pain.

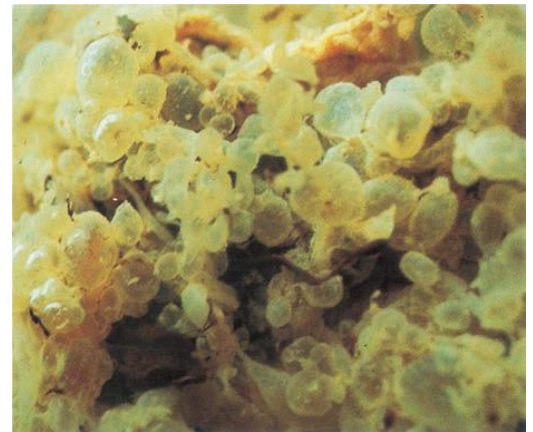
Exploratory laparotomy reveals rupture of the posterior uterine fundus with grape-like tissue extruding from the defect. Two liters of blood are present in the abdominal cavity. Histologic examination of the uterine mass is shown in the image. The arrows point to syncytial cells. Which of the following is the most likely diagnosis?

- (A) Carcinosarcoma
- (B) Choriocarcinoma
- (C) Embryonal carcinoma
- (D) Endometrial adenocarcinoma
- (E) Yolk sac carcinoma



3- A 17-year-old woman presents to her gynecologist with a 5-day history of vaginal bleeding. A home pregnancy test had been positive 1 week previously. This morning, the patient passed tissue with the appearance of small grapes. An ultrasound shows a dilated endometrial cavity but no evidence of a fetus. Endometrial evacuation of the uterus by suction curettage reveals grapelike clusters, with individual units measuring up to 5 mm in diameter (shown in the image). Cytogenetic examination of this tissue will most likely demonstrate which of the following genetic patterns?

- (A) Aneuploidy
- (B) Diploidy
- (C) Haploidy
- (D) Polyploidy
- (E) Triploidy



4- A 22-year-old woman presents to the emergency room with a 2-hour history of acute abdominal pain and vaginal bleeding. Her vital signs are normal. Physical examination reveals blood oozing from the vaginal opening. Laparotomy shows an enlarged right fallopian tube with hemorrhage and rupture. What is the most likely cause of hemorrhage in this patient?

- (A) Choriocarcinoma

- (B) Ectopic pregnancy
- (C) Infarcted tubal polyp
- (D) Intramural leiomyoma
- (E) Tubal adenocarcinoma

5- A 60-year-old woman presents with a 2-week history of uterine bleeding. Gynecologic examination reveals an enlarged uterus. The hysterectomy specimen shows a large polypoid mass involving the endometrium and myometrium. Histologic examination reveals malignant glands and malignant stromal elements, including striated muscle and cartilage. What is the appropriate diagnosis?

- (A) Carcinosarcoma
- (B) Endometrioid adenocarcinoma
- (C) Leiomyosarcoma
- (D) Pleomorphic adenoma
- (E) Rhabdomyosarcoma

1- **The answer is E: Triploidy.** Cytogenetic examination of a partial hydatidiform mole will reveal triploidy. This abnormal chromosomal complement results from the fertilization of a normal ovum (23,X) by two normal spermatozoa, each carrying 23 chromosomes, or a single spermatozoon that has not undergone meiotic reduction and bears 46 chromosomes. The fetus associated with a partial mole usually dies after 10 weeks of gestation, and the mole is aborted shortly thereafter. In contrast to a complete mole, which exhibits diploidy (choice B), fetal parts are commonly present in a partial hydatidiform mole.

Diagnosis: Partial hydatidiform mole

2- **The answer is B: Choriocarcinoma.** Choriocarcinoma occurs in 1 in 30,000 pregnancies in the United States. In Asia, the frequency is far greater. Choriocarcinoma develops in about 2% of patients after a complete hydatidiform mole has been evacuated. Abnormal uterine bleeding is the most frequent initial indication that heralds choriocarcinoma. Occasionally, the first sign relates to metastases to the lungs or brain. In some cases, choriocarcinoma only becomes evident 10 or more years after the last pregnancy. The other choices are not sequelae of gestational trophoblastic disease.

Diagnosis: Choriocarcinoma

3- **The answer is B: Diploidy.** The term gestational trophoblastic disease embraces the spectrum of trophoblastic disorders that exhibit abnormal proliferation and maturation of trophoblast, as well as neoplasms derived from the trophoblast. Complete hydatidiform mole is a placenta that has grossly swollen chorionic villi, resembling bunches of grapes, in which there are varying degrees of trophoblastic proliferation. Complete mole results from the fertilization of an empty ovum that lacks functional DNA. The haploid (23,X) set of paternal chromosomes duplicates to 46,XX. Hence, most complete moles are homozygous 46,XX, but all of the chromosomes are of paternal origin. Since the embryo dies at a very early stage, fetal parts are absent. Malignant transformation (choriocarcinoma) develops in about 2% of cases. Triploidy (choice E) is encountered in partial hydatidiform mole, but this diagnosis is ruled out by the absence of fetal tissue.

Diagnosis: Complete hydatidiform mole

4- **The answer is B: Ectopic pregnancy.** Over 95% of ectopic pregnancies occur in the fallopian tube. Ectopic pregnancy results when the passage of the conceptus along the fallopian tube is impeded, for example, by mucosal adhesions or abnormal tubal motility secondary to inflammatory disease or endometriosis. The trophoblast readily penetrates the mucosa and tubal wall. The thin tubal wall usually ruptures by the 12th week of gestation. Tubal rupture is life threatening because it can result in rapid exsanguination. The other choices are rare.

Diagnosis: Ectopic pregnancy

5- **The answer is A: Carcinosarcoma.** Carcinosarcoma is an aggressive, mixed mesodermal tumor, in which the epithelial and stromal components are both highly malignant. These neoplasms are derived from multipotential stromal cells. The overall 5-year rate survival is 25%. Pleomorphic adenoma (choice D) is a mixed tumor of salivary gland. The other choices do not feature biphasic components.

Diagnosis: Carcinosarcoma

Old MCQs

1. A 26-year-old female acutely develops lower abdominal pain and vaginal bleeding. While in the bathroom she passes a cast of tissue composed of clot material and then collapses. She is brought to the hospital, where a physical examination reveals a soft, tender mass in right adnexa and pouch of Douglas. Histologic examination of the tissue passed in the bathroom reveals blood clots and decidualized tissue. No chorionic villi or trophoblastic tissue are present. Which one of the following conditions is most likely present in this individual?

- a. Aborted intrauterine pregnancy
- b. Complete hydatidiform mole
- c. Ectopic pregnancy
- d. Endometrial hyperplasia
- e. Partial hydatidiform mole

2. A 25-year-old woman in her fifteenth week of pregnancy presents with uterine bleeding and passage of a small amount of watery fluid and tissue. She is found to have a uterus that is much larger than estimated by her gestational dates. Her uterus is found to be filled with cystic, avascular, grapelike structures that do not penetrate the uterine wall. No fetal parts are found. The most likely diagnosis for this abnormality is :

- a. Partial hydatidiform mole
- b. Complete hydatidiform mole
- c. Invasive mole
- d. Placental site trophoblastic tumor
- e. Choriocarcinoma

3. In complete hydatiform mole , which is correct:

- A- Chromosomal analysis shows 69XXY
- B- Uterus is small
- C- Presence of embryonic tissue
- D- Elevated HCG (very high)

4. Regarding GTD (gestational trophoblastic disease) which of the following is correct :

- A- Majority are benign
- B- Women who have GTD can have normal pregnancies later
- C- HCG is mostly used to diagnoses
- D- All of the above

5. Which one of these best describes ectopic pregnancy :

- a. Implantation of the blastocyst in the any other site than the endometrium

- b. Fertilization of the ovum in the uterine cavity
- c. A pregnancy is only considered ectopic if the implantation occurs in the ovary
- d. Implantation in the endometrium

6. Regarding spontaneous abortions :

- a. The embryo is lost in time period prior to his 20th week of life
- b. Most common complication of early pregnancy
- c. Can occur during to systemic diseases like SLE (systemic lupus)
- d. All of the above

1:C 2:B 3:D 4:D 5:A 6:D