

# **Ectopic Pregnancy, Spontaneous Abortion And Gestational Trophoblastic Disease.**

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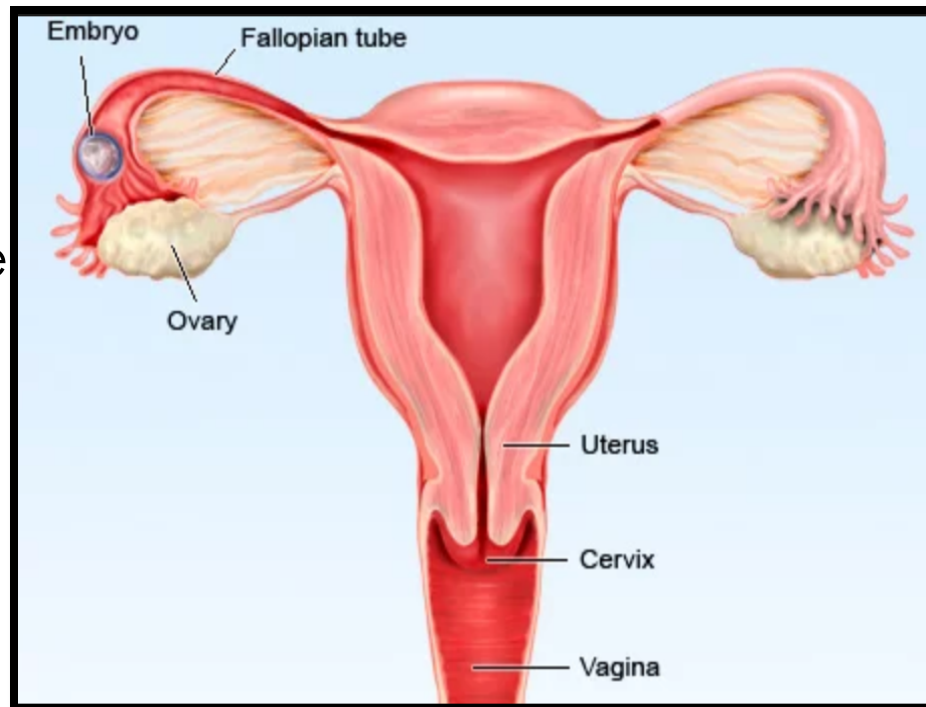
# Objectives

At the end of this lecture, the student should be able to:

- A. Understand the pathology and predisposing factors of ectopic pregnancy and spontaneous abortion.
- B. Know the clinical presentation and pathology of hydatidiform mole and choriocarcinoma.

# Ectopic Pregnancy

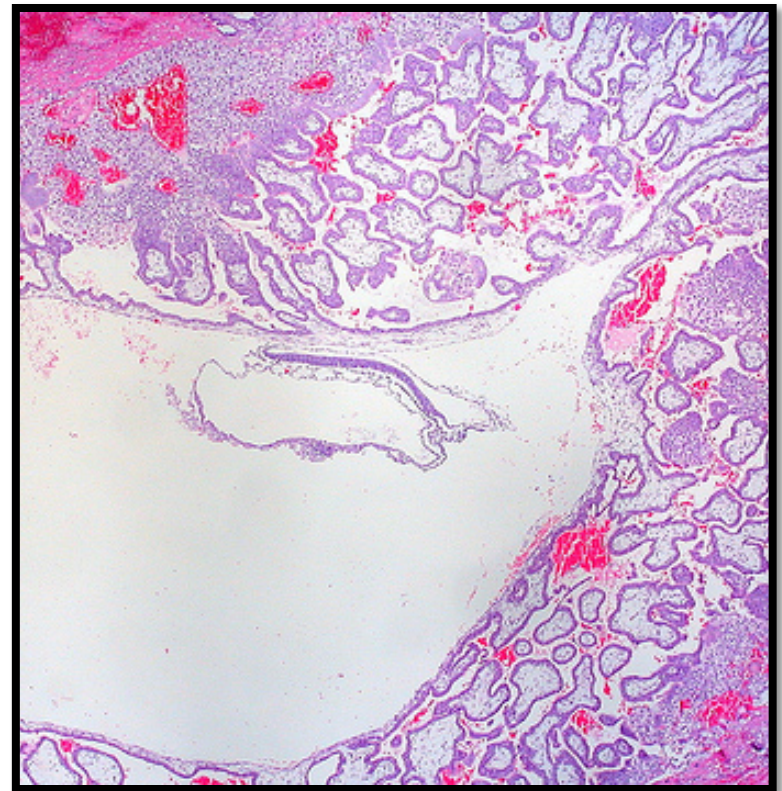
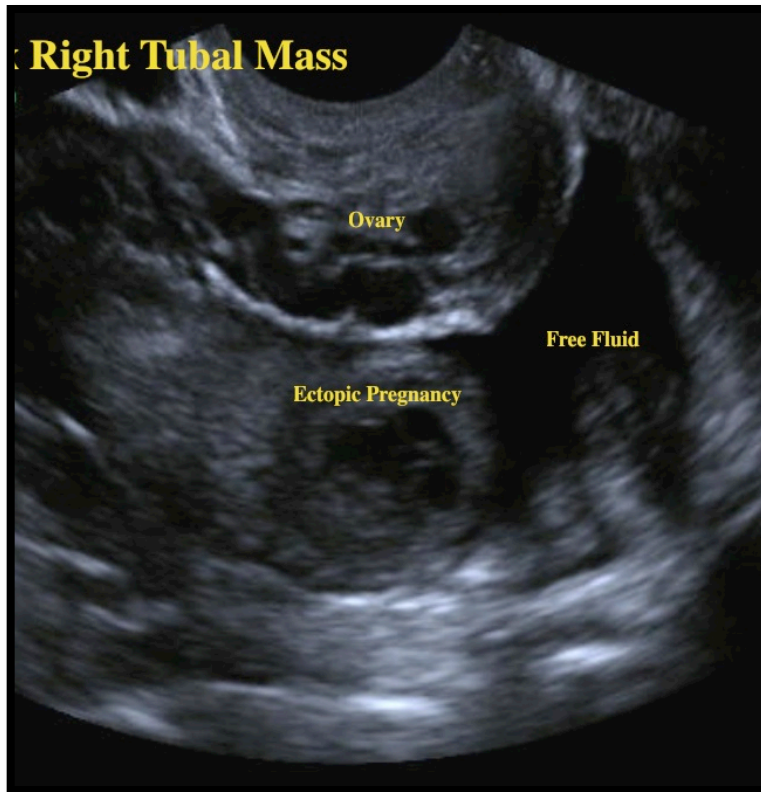
- Ectopic pregnancy is defined as implantation of a fertilized ovum in any site other than the endometrium of the uterine cavity.
- About 1% of all pregnancies are ectopic.
- Sites:
  - Over 90% of ectopic pregnancies occur in the fallopian tubes (tubal pregnancy).
  - Other sites include: ovaries, abdominal cavity and cervix.



# Clinical Features

- A woman with an ectopic tubal pregnancy may present with pelvic pain or abnormal bleeding following a period of amenorrhea.
- Many present as an emergency with tubal rupture, severe acute abdominal pain and hemorrhagic shock.
- The diagnosis is usually confirmed by an abdominal/pelvic ultrasound → gestational sac within fallopian tube or other location and a positive pregnancy test (high HCG levels).
- Microscopically: placental tissue or fetal parts within the tube.

# Clinical Features



# Risk Factors

- Any factor that retards passage of the ovum through the tubes predisposes to tubal ectopic pregnancy.
- In about half of the cases, it is due to chronic inflammation and scarring of the oviduct.

# Risk Factors

- Pelvic inflammatory diseases/infections/salpingitis: are the most common causes. The inflammation can damage the ciliary activity and cause tubal obstruction, pelvic adhesions with scarring and distortion of the fallopian tubes. Women who have had pelvic infections have a five times greater risk of ectopic pregnancy (infection is usually by *Neisseriae Gonorrhoea* or *Chlamydia*).
- Abdominal/pelvic surgery or tubal ligation surgery.
- Intrauterine tumors and endometriosis.
- Smoking can decrease tubal motility by damaging the ciliated cells or it may predispose them to pelvic inflammatory diseases (due to the impaired immunity in smokers).

# Risk Factors

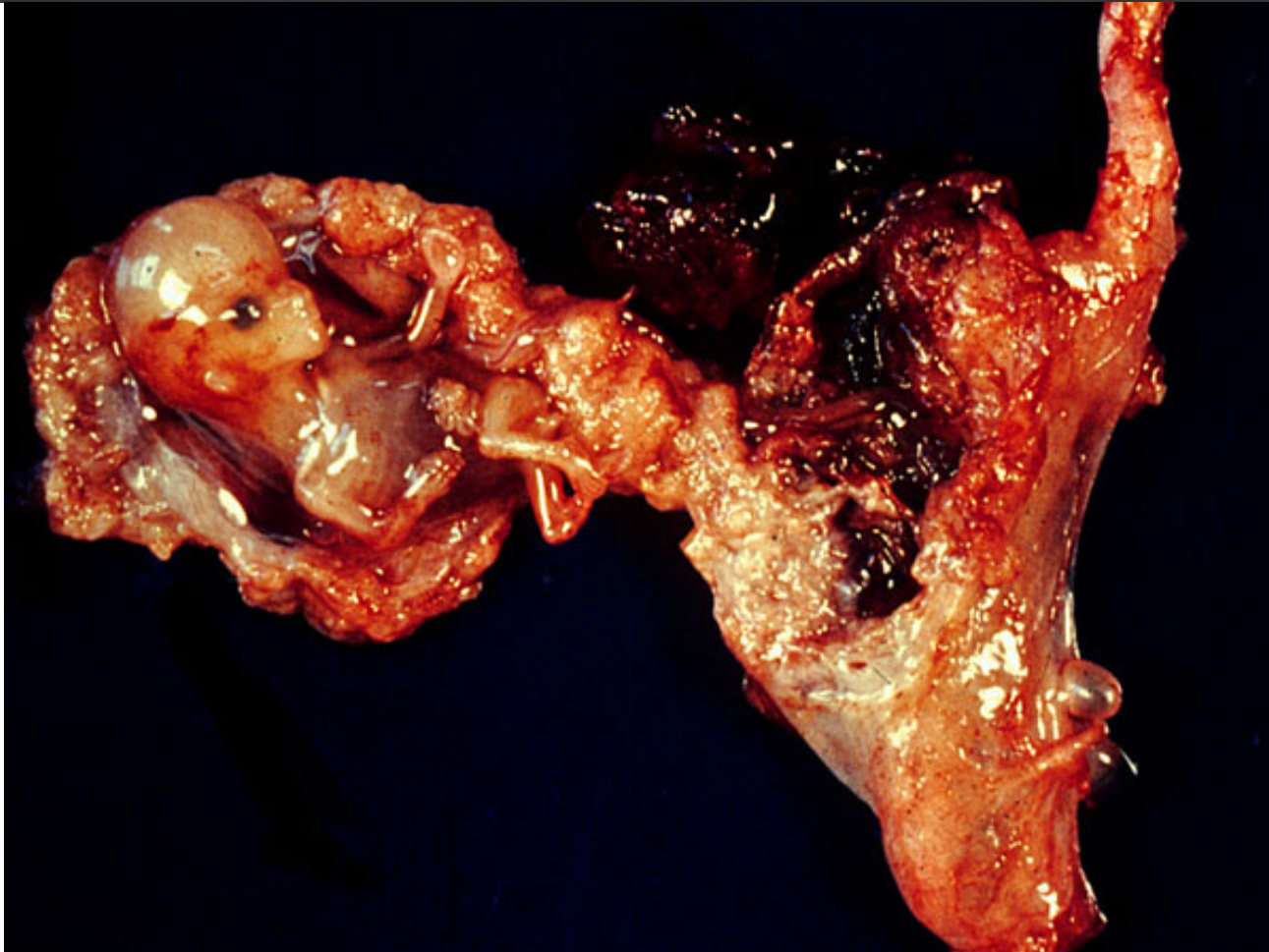
- ❑ Congenital anomaly of the tubes.
- ❑ In-utero diethylstilbestrol (DES) exposure increases the risk of ectopic pregnancy due to abnormal tubal morphology.
- ❑ History of previous ectopic pregnancy.
- ❑ History of multiple sexual partners → increases the chance of pelvic inflammatory diseases and therefore are high risk for ectopic pregnancies.
- ❑ Intrauterine device users are at higher risk of having an ectopic pregnancy should pregnancy occurs.



# Risk Factors

- History of infertility: there is higher risk of ectopic pregnancy in the infertile population. This may be due to the underlying infertility related issues or fertility drugs and treatments. In vitro fertilization has been associated with an increased risk of ectopic pregnancy including cervical pregnancies.
- Please note that in many tubal pregnancies, no anatomic cause is evident.
- Ovarian pregnancies probably result from rare instances in which the ovum is fertilized just as the follicle ruptures.
- Gestation within the abdominal cavity occurs when the fertilized egg drops out of the fimbriated end of the oviduct and implants on the peritoneum.

# Ectopic Pregnancy



# Spontaneous Abortion/Miscarriage

- It is the spontaneous end of a pregnancy at a stage where the embryo or fetus is incapable of surviving.
- Miscarriages that occur:
  - before the 6th week of gestation are called early pregnancy loss or chemical pregnancy.
  - after the 6th week of gestation are called clinical spontaneous abortion.
- About 10-25% of all pregnancies end in a miscarriage.
- Most miscarriages occur during the first 13 weeks of pregnancy.

# Causes of Spontaneous Abortions/Miscarriages

- Most miscarriages occur during the first trimester.
- The cause of a miscarriage cannot always be determined.
- Miscarriages can occur for many reasons.
- Chromosomal abnormalities of the fetus are the most common cause of early miscarriages.



# Causes of Spontaneous Abortions/Miscarriages

- Chromosomal abnormalities:
  - Half of the 1st trimester miscarriages have abnormal chromosomes.
  - Chromosomal abnormalities also become more common with age, and women over the age of 35 have a higher rate of miscarriage than younger women.
  - A pregnancy with a genetic problem has a 95% probability of ending in a miscarriage.

# Causes of Spontaneous Abortions/Miscarriages

- Hormonal problems: there is an increased risk of a miscarriage with:
  - Cushing's Syndrome
  - Thyroid diseases
  - Polycystic ovary syndrome
  - Diabetes: good control of blood sugar during pregnancy is important. If the diabetes is not well controlled, there is an increase risk of miscarriages and also of the baby having birth defects.
  - Inadequate function of the corpus luteum in the ovary (which produces the progesterone necessary for maintenance of the very early stages of pregnancy) leads to progesterone deficiency which may lead to a miscarriage.

# Causes of Spontaneous Abortions/Miscarriages

- Infections: by *Listeria Monocytogenes*, *Toxoplasma Gondii*, Parvovirus B19, Rubella, Herpes Simplex, Cytomegalovirus and lymphocytic choriomeningitis virus etc are associated with an increased risk of pregnancy loss.
- Maternal health problems can predispose to miscarriages e.g. systemic lupus erythematosus and antiphospholipid antibody syndrome

# Causes of Spontaneous Abortions/Miscarriages

- Lifestyle: smoking, drug use, malnutrition and exposure to radiation or toxic substances.
- Maternal age: Miscarriages increase after the age of 35 due to ovum abnormalities.
- Maternal trauma.



# Causes of Spontaneous Abortions/Miscarriages

- Abnormal structural anatomy of the uterus can also cause miscarriages e.g. septate or bicornate uterus affect placental attachment and growth. Therefore, an embryo implanting on the septum would be at increased risk of a miscarriage. Uncommonly uterine fibroids can interfere with the implantation and blood supply, thereby causing a miscarriage.
- Others: surgical procedures in the uterus during pregnancy e.g. amniocentesis and chorionic villus sampling.

# Causes of Spontaneous Abortions/Miscarriages

SEPTATE



Wedge of fibrous tissue dividing uterine cavity.

ASHERMAN'S SYNDROME



Adhesions (band-like formations) crossing the lining of the uterus.

BICORNATE UTERUS



Incomplete uniting of uterus.

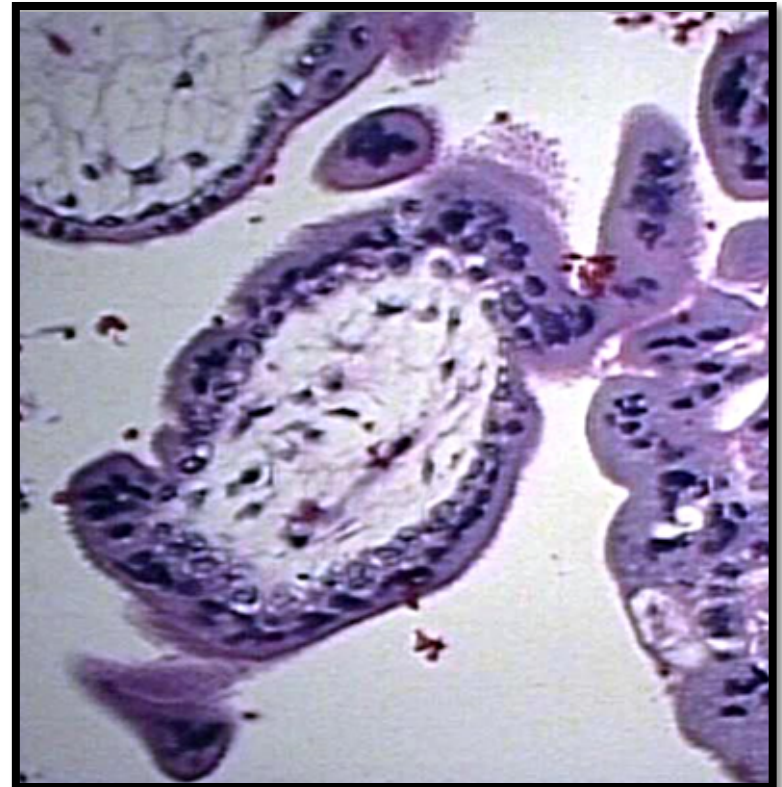
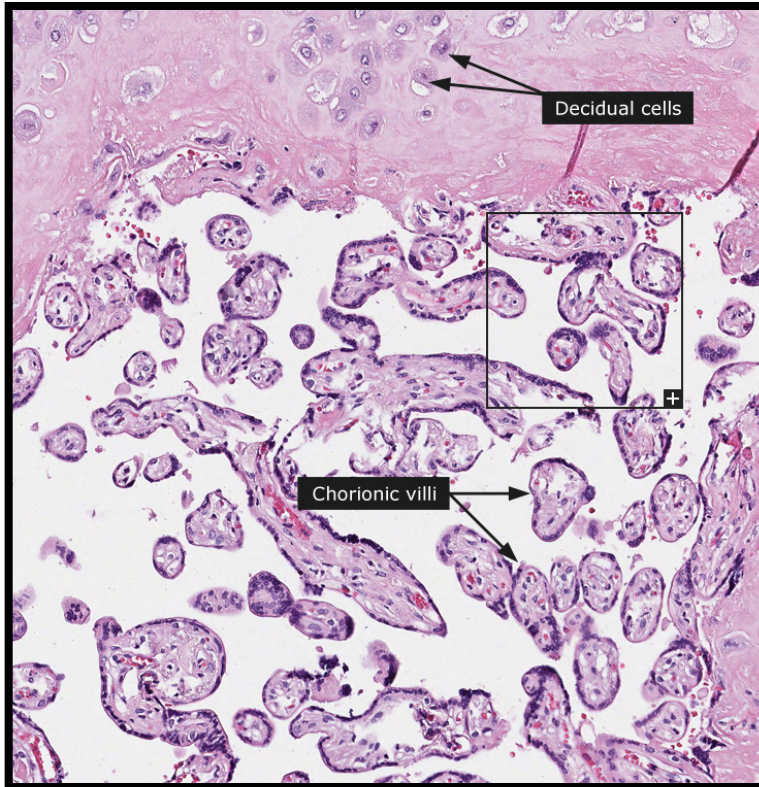
# Diagnosis of Spontaneous Abortions/Miscarriages

- A miscarriage can be confirmed:
  - By ultrasound
  - By the examination of the passed tissue microscopically for products of conception. The products of conception include chorionic villi, trophoblasts, fetal parts and changes in the endometrium (hypersecretory).
  
- Genetic tests may also be performed to look for chromosomal anomalies.

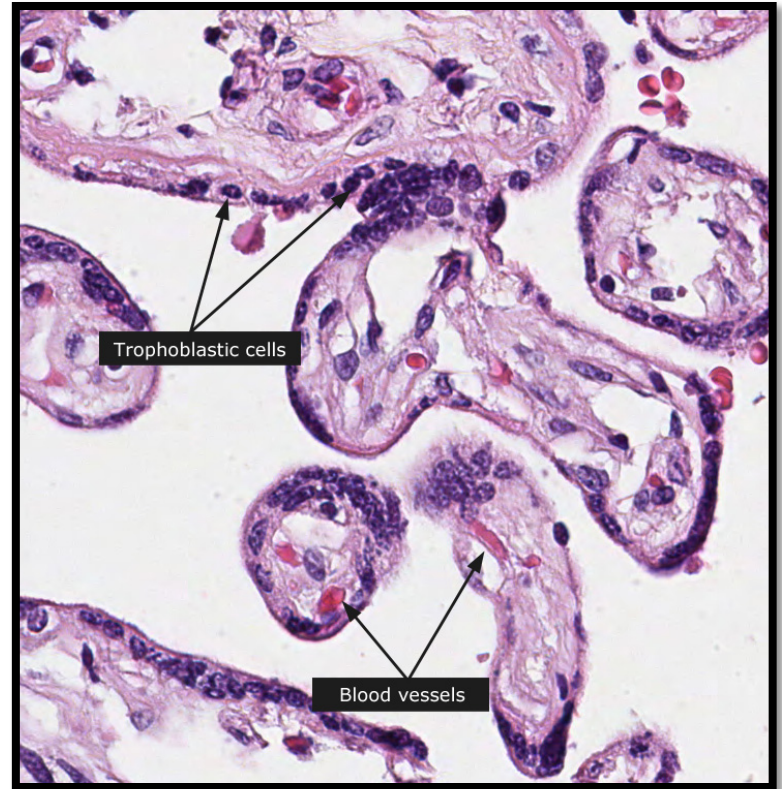
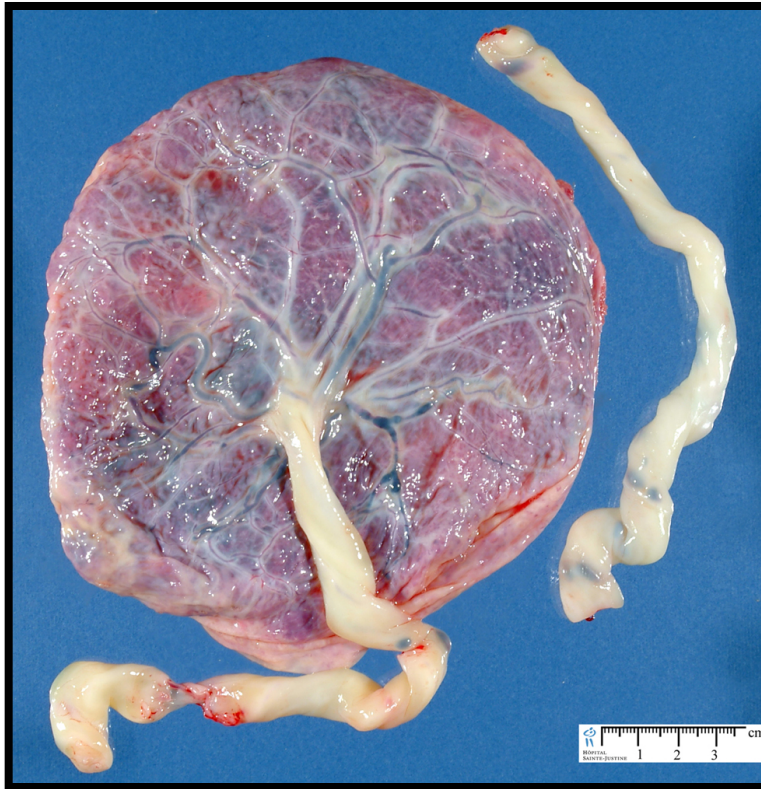
# Products of Conception



# Products of Conception

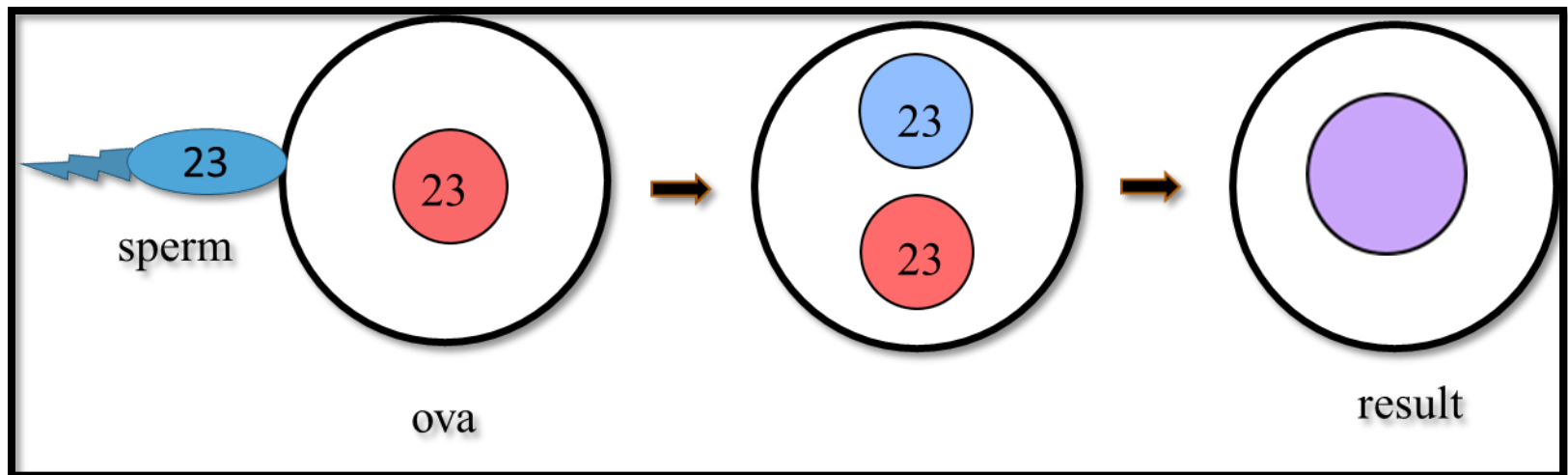


# Normal Placenta



# Normal Fertilization

- Normal fertilization: a single sperm of 23 chromosomes fertilizes a normal egg of 23 chromosomes



# Types of Gestational Trophoblastic Diseases

- Benign non-neoplastic trophoblastic lesions — diagnosed as incidental findings in an endometrial curettage or hysterectomy specimen.
  - Exaggerated placental site
  - Placental site nodule
  
- Hydatidiform mole — result from abnormalities in fertilization. They are essentially benign, but these patients carry an increased risk of subsequently developing choriocarcinoma.
  - Complete hydatidiform mole
  - Partial hydatidiform mole
  - Invasive mole/chorioadenoma destruens
  
- Gestational trophoblastic neoplasia (GTN) — are a group of tumors. They have potential for local invasion and metastases.
  - Choriocarcinoma
  - Placental site trophoblastic tumor
  - Epithelioid trophoblastic tumor



# Hydatidiform Mole

- It is an abnormal placenta due to the excess of paternal (from father) genes.
- It is caused by abnormal gametogenesis and fertilization.
- It is the most common form of gestational trophoblastic disease; occurs in 1/1,000-2,000 pregnancies.
- It results in the formation of enlarged and edematous placental villi, which fill the lumen of the uterus.
- Passage of tissue fragments, which appear as small grapelike masses, is common. Serum HCG concentration is markedly elevated, and they rapidly increase.

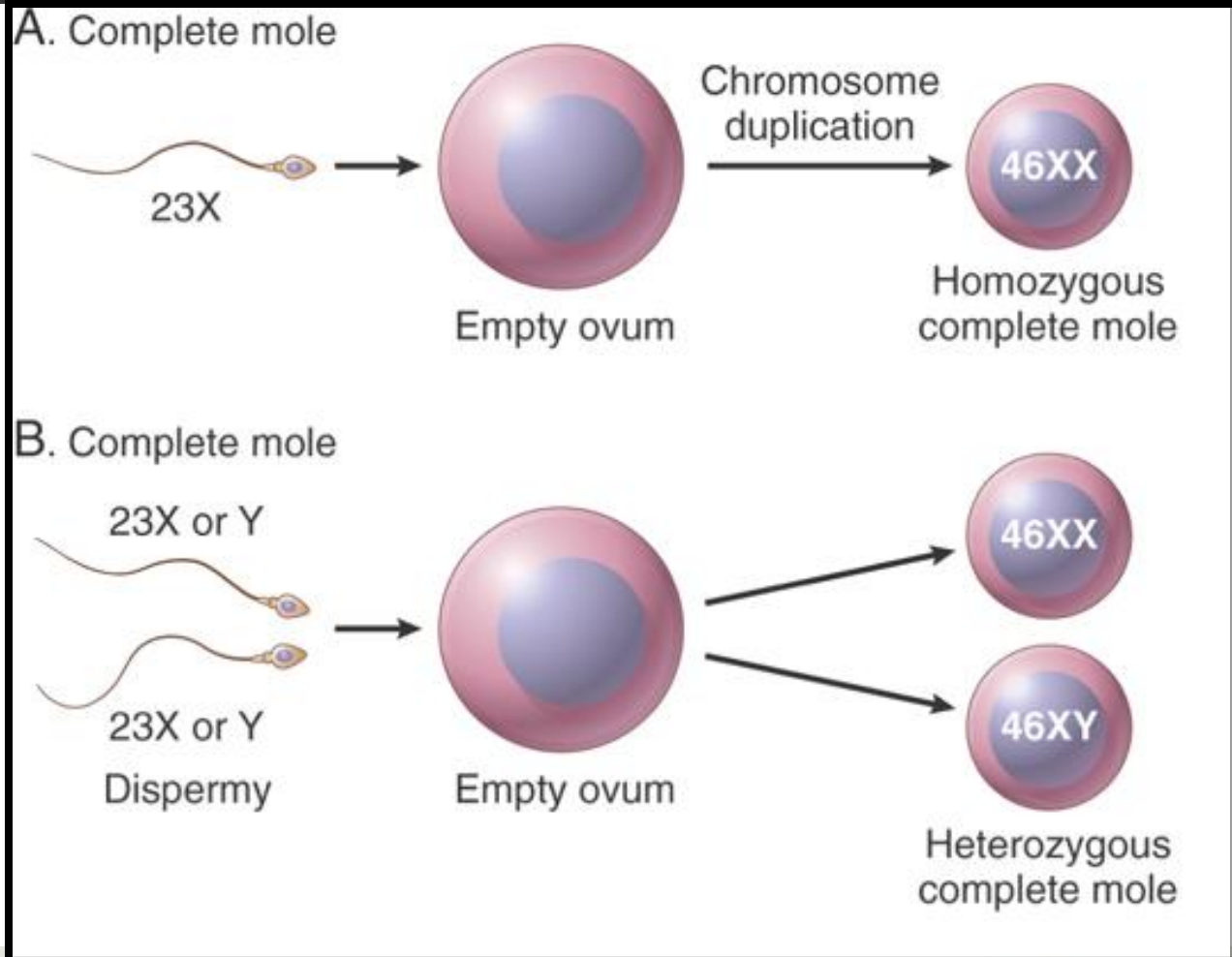
# Hydatidiform Mole

- **Risk factors:**
  - maternal age: girls younger than 15 years of age and women over 40 are at higher risk.
  - Ethnic background: high in Asian women.
  - Women with a prior hydatidiform mole have a 20-fold greater risk of a subsequent molar pregnancy than the general population.
  
- There are 2 types of hydatidiform mole (HM).
  - **Complete HM**
  - **Partial HM**

# Complete HM

- It results from the fertilization of an empty ovum that lacks maternal DNA  
→ as a result all chromosomes are derived from the sperm.
- There is complete lack of maternal chromosomes. All the chromosomes come from the male/paternal side i.e. it is an androgenetic pregnancy with no maternal DNA.
- 90% of complete moles are 46 XX, arising from duplication of the chromosomes of a haploid sperm after fertilization of an empty ovum. 10% of cases are 46 XY as a result of fertilization of an empty ovum by 2 sperms (dispermy).

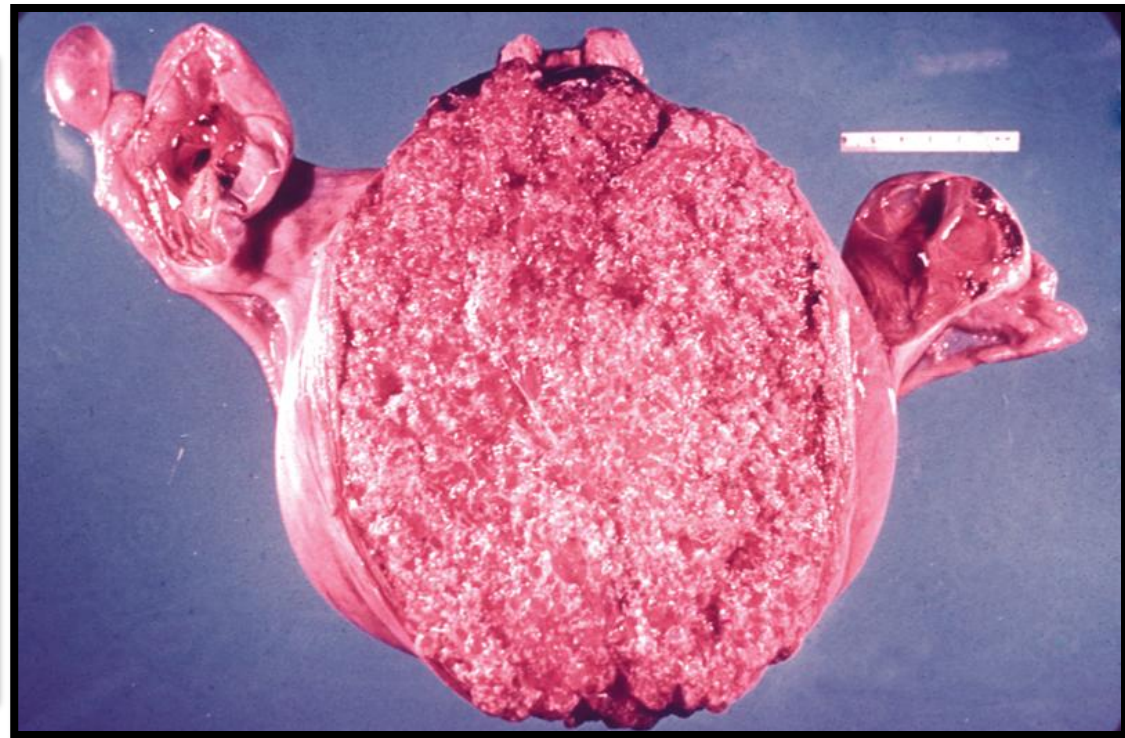
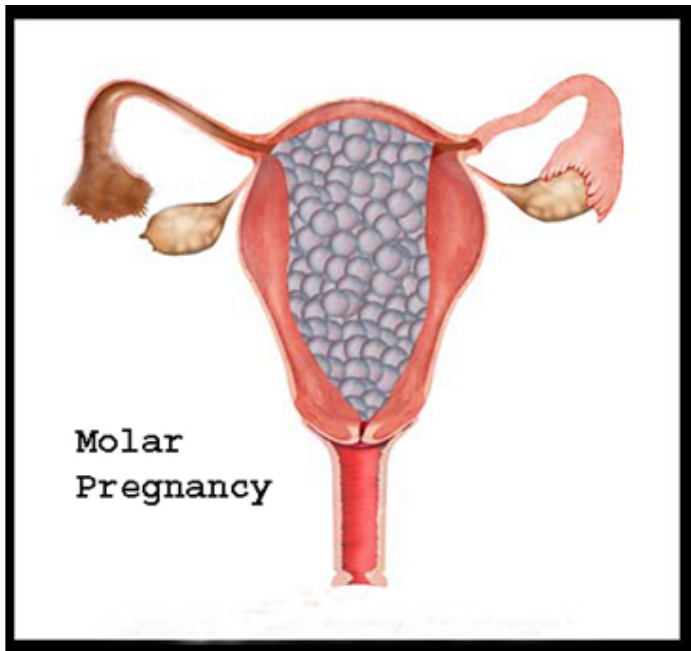
# Complete HM



# Complete HM

- The uterus is distended and filled with swollen/large villi with prominent trophoblastic cells proliferation. No embryo, or fetal tissue is present. Grossly it looks like a bunch of grapes.
- It is a genetically abnormal placenta with hyperplastic trophoblasts, without a fetus or an embryo.

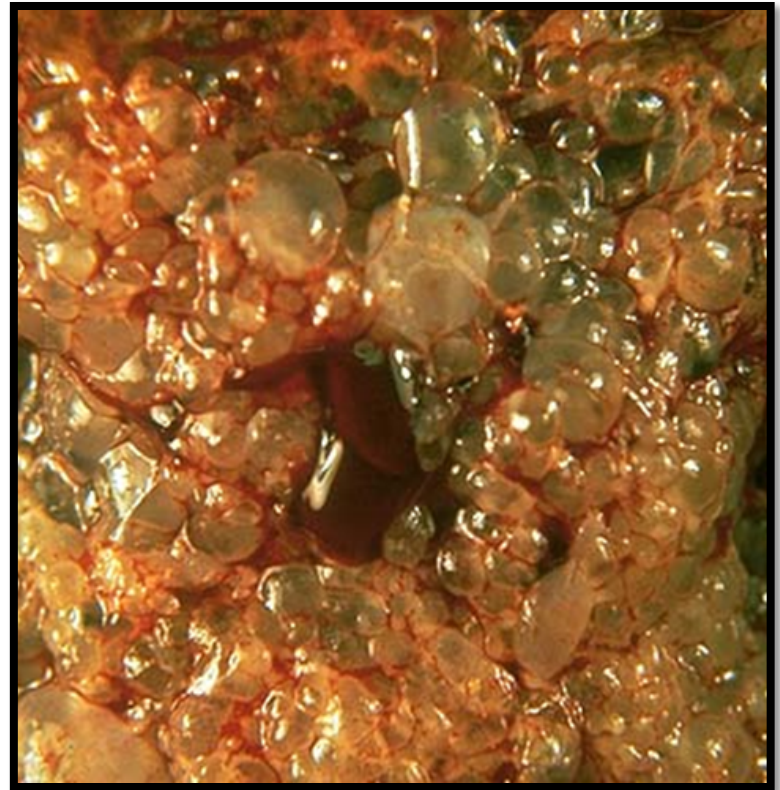
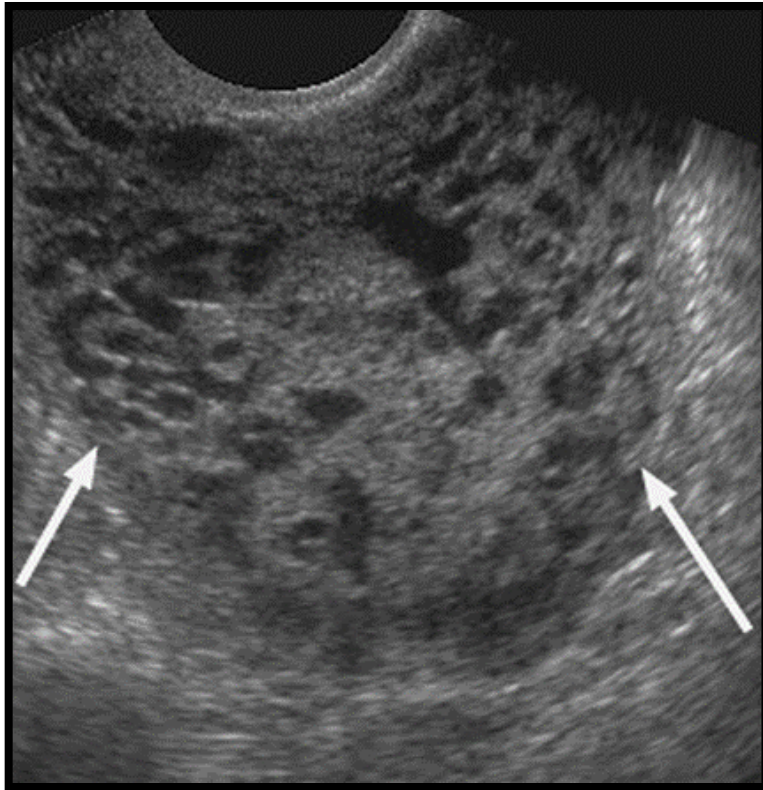
# Complete HM



# Complete HM

- **Symptoms:** rapid abdominal swelling (due to a rapid increase in uterine size) mistaken for a normal pregnancy but the uterus is disproportionately large for that stage of pregnancy. In addition patient may have vaginal bleeding, severe nausea and vomiting. HCG levels are elevated.
- **Ultrasound:** it shows a “cluster of grapes” appearance or a “snowstorm” appearance, signifying an abnormal placenta.

# Complete HM





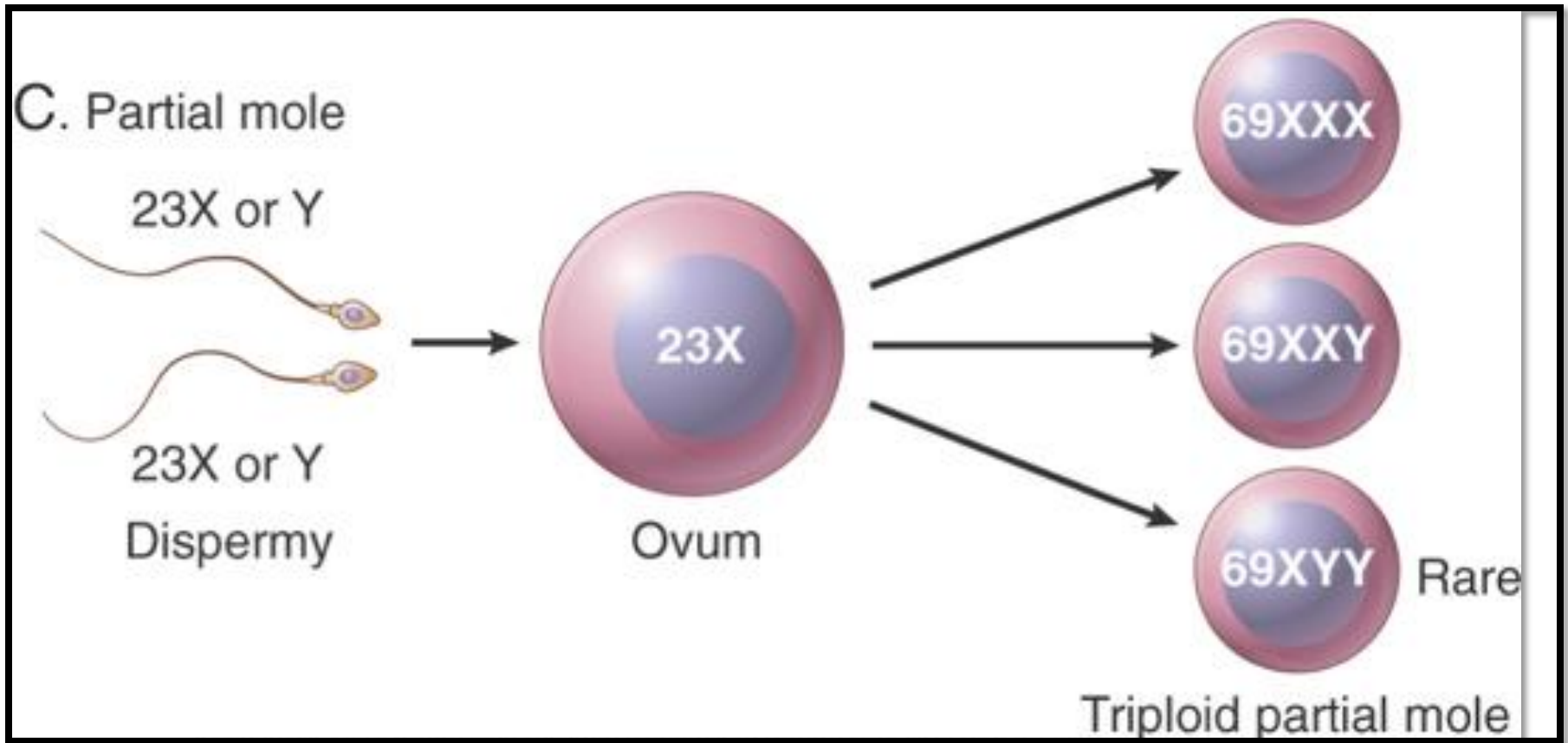
# Complete HM

- **Complications:** uterine hemorrhage, uterine perforation, trophoblastic embolism, and infection. Few patients develop an invasive mole. The most important complication is the development of choriocarcinoma, which occurs in about 2% of patients after the mole has been evacuated.
- **Treatment:** Evacuation of uterus by curettage and sometimes chemotherapy. With appropriate therapy, cure rates are very high.

# Partial HM

- Partial HM results from the fertilization of a normal ovum (that has not lost its maternal chromosomes) by 2 normal sperms. This results in a triploid cell having 69 chromosomes (triploidy gestation), of which one haploid set (23X) is maternal and two haploid (23+23=46) sets are paternal in origin (58% are 69XXY, 40% are 69XXX, 2% are 69XYY).
- It almost never evolves into choriocarcinoma.

# Partial HM



# Partial HM

- It is a genetically abnormal placenta with a resultant mixture of large and small villi and slight hyperplasia of the trophoblasts, filling the uterus. In contrast to a complete mole, embryo/fetal parts may be present. But the fetus associated with a partial mole usually dies after 10 weeks gestation and the mole (~pregnancy) is aborted shortly thereafter.
- Grossly the genetically abnormal placenta has a mixture of large chorionic villi and normal-appearing smaller villi.

# Partial HM

- It makes up to 15–35% of all moles
- The uterine size is usually small or appropriate for the gestational age
- Serum HCG levels are high but not as high as complete mole.
- Chromosomal analysis of partial moles shows 69XXY in the majority of cases (i.e. 3 haploid sets also called as triploidy).

# Partial HM

- **Treatment:** Evacuation of the uterus by curettage and sometimes chemotherapy.
- **Prognosis:** The risk for developing choriocarcinoma is very low but follow-up is mandatory.

<b>FEATURE</b>	<b>CM</b>	<b>PM</b>
Karyotype	Usually diploid 46XX	Usually triploidy 69XXY (most common)
Villi	All villi are hydropic; no normal villi seen	Normal villi may be present
Fetal tissue	Not present	Usually present
Trophoblasts	Marked proliferation	Mild proliferation
Serum HCG	Markedly elevated	Less elevated
Invasive mole	Occurs in about 15% of CMs	Very rare
Behavior	2% progress to choriocarcinoma	Very rarely progress to choriocarcinoma

# Invasive Mole

- Invasive mole is when the villi of a hydatidiform mole extends/infiltrates into the myometrium of the uterus.
- The mole sometime enters into the veins in the myometrium, and spreads via vascular channels to distant sites, mostly the lungs (note: death from such spread is unusual).
- It occurs in about 15% of complete moles and rarely in partial mole.
- It can cause hemorrhage and uterine perforation.



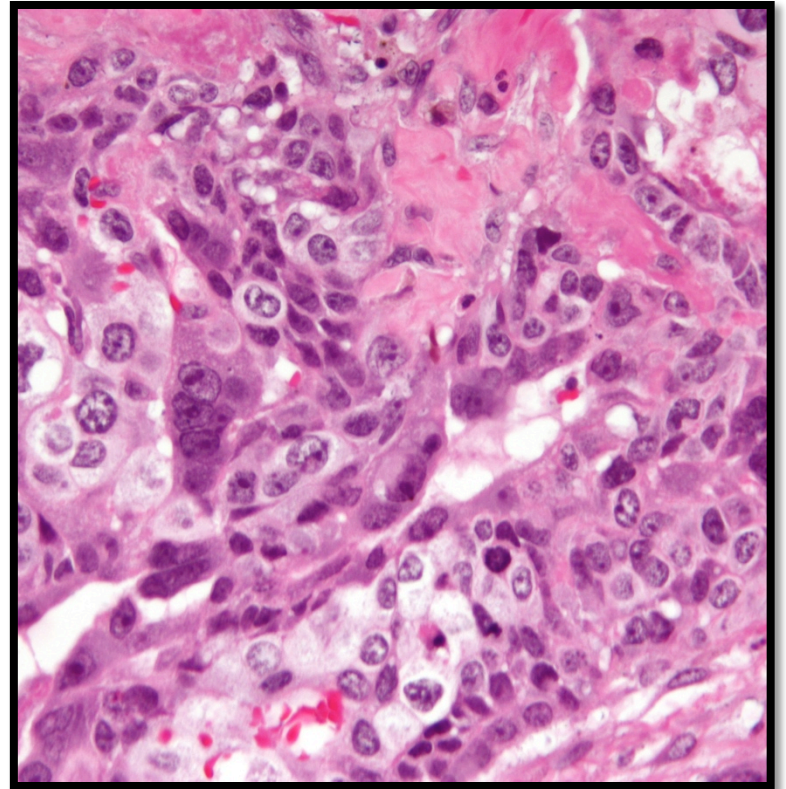
# Choriocarcinoma

- **Definition:** It is a malignant tumor of placental tissue, composed of a proliferation of malignant cytotrophoblasts and syncytiotrophoblasts, without villi formation.
- It is an aggressive malignant neoplasm.
- It is characterized by very high levels of serum HCG.
- Choriocarcinomas are aneuploidic.

# Choriocarcinoma

- It spreads early via blood to the lungs and other organs.
- It responds to chemotherapy.
- About half of choriocarcinoma cases are preceded by complete hydatidiform mole. Others can be preceded by a partial mole (rare), abortion, ectopic pregnancy and occasionally a normal term pregnancy.

# Choriocarcinoma





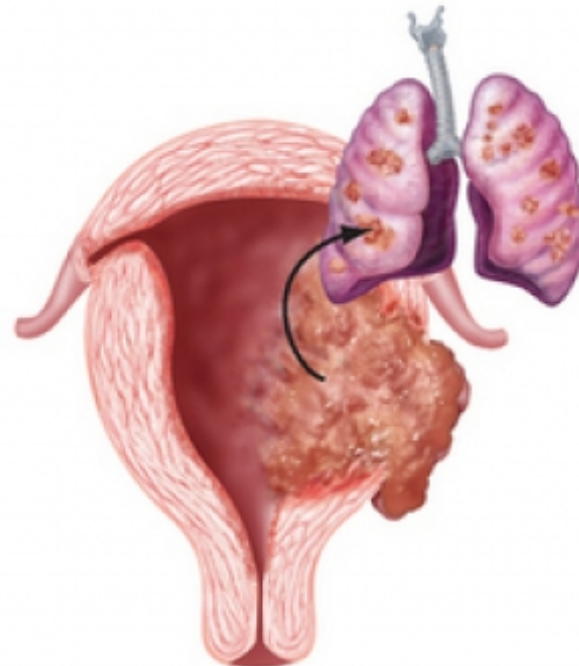
Complete hydatidiform mole



Partial hydatidiform mole



Invasive mole



Choriocarcinoma

# Reference

- Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 10<sup>th</sup> ed. Elsevier; 2018. Philadelphia, PA.

# Thank You

End of Lecture