



Lecture 6: Disorders of Pregnancy & Placenta

(Pathology of ectopic pregnancy, spontaneous abortion, and gestational trophoblastic disease)



Objectives:

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



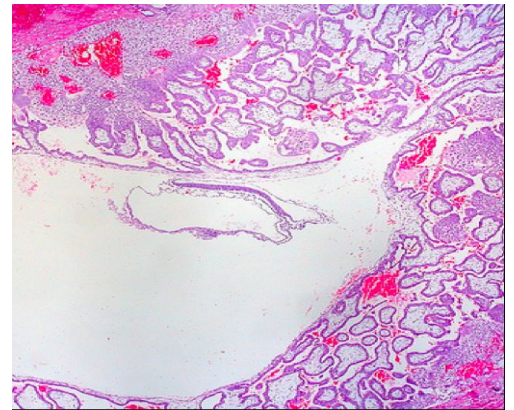
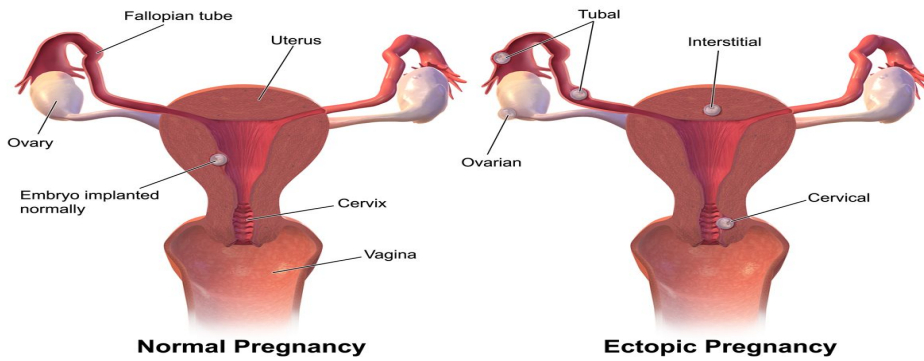
MED437
KING SAUD UNIVERSITY



Important
Terminology
Doctor's Notes
Extra Information

Ectopic pregnancy

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 of ectopic pregnancy include the ovaries, abdominal cavity and uterine 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.

Diagnosis:

Clinical:

- Abdominal/pelvic ultrasound → gestational sac within fallopian tube or other location.
- Positive HCG levels .

Microscopic:

- Placental tissue or fetal parts **within the tube.**

Tubal ectopic pregnancy:

- Fallopian tubes are the most common location for ectopic pregnancies
- 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** in the oviduct.

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.

Risk factor for ectopic pregnancy

1. **Pelvic inflammatory disease**/infections/salpingitis (**inflammation of the fallopian tubes**) is the most common cause. The inflammation can damage ciliary activity, 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* & *chlamydia*).
2. Abdominal/pelvic surgery or tubal ligation surgery (previous surgery). (e.g. **appendicitis**)
3. Intrauterine tumors and endometriosis.
4. Smoking can decrease tubal motility by damaging ciliated cells or it to pelvic inflammatory disease (due to the impaired immunity in smokers).
5. **Congenital anomaly of the tubes.**
6. **Intrauterine contraceptive device (IUCD)** are at higher risk of having an ectopic pregnancy should pregnancy occur.
7. History of previous ectopic pregnancy.
8. **In-utero diethylstilbestrol (DES) exposure increases the risk of ectopic pregnancy due to abnormal tubal morphology.**
9. History of multiple sexual partners increases chance of pelvic inflammatory disease and therefore are high risk for ectopic pregnancy.
10. 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

SPONTANEOUS ABORTION

Spontaneous abortion (SAB)/ Miscarriage

- **Also known as 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 miscarriage.
- Most miscarriages occur during the **first 13 weeks** (first trimester) of pregnancy.



Causes of SAB/Miscarriage:

- 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.

The causes are as follows

1. Chromosomal abnormalities: (Most common cause)

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

2. Hormonal problems: there is an increased risk of miscarriage with

- Cushing's Syndrome.
- Thyroid disease.
- Polycystic ovary syndrome (PCOS).
- Diabetes: good control of blood sugars during pregnancy is important. If the diabetes is not well controlled, there is increase risk of miscarriages and also of the baby to have birth defects.
- 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.

3. 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.

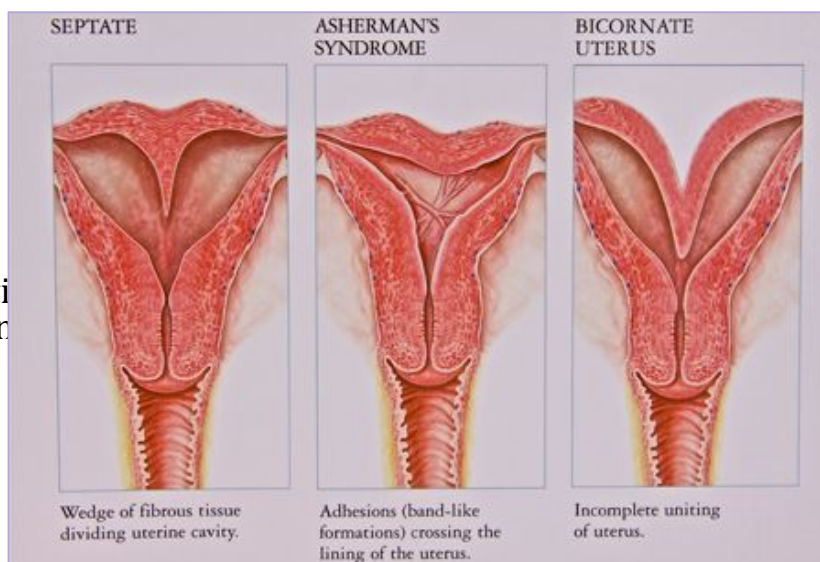
4. Maternal health problems can predispose to miscarriages e.g. systemic lupus erythematosus and antiphospholipid antibody syndrome.

5. Lifestyle: smoking, drug use, malnutrition and exposure to radiation or toxic substances.

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

7. Maternal trauma.

8. 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 miscarriage. Uncommonly uterine fibroids can interfere with the embryo implantation and blood supply, thereby causing miscarriage.



9. Others: surgi
and chorion

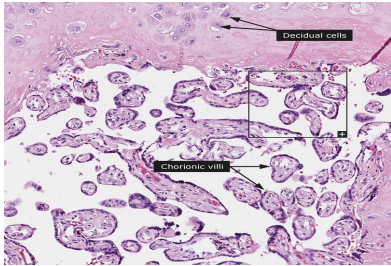
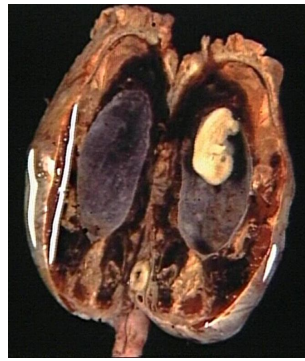
amniocentesis

SAB/miscarriage

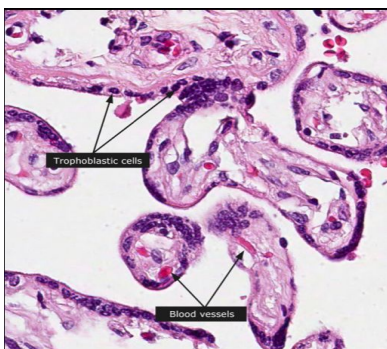
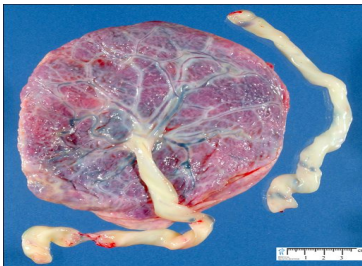
Diagnosis:

- A miscarriage can be confirmed:
 - By ultrasound study.
 - By the examination of the passed tissue microscopically for the 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

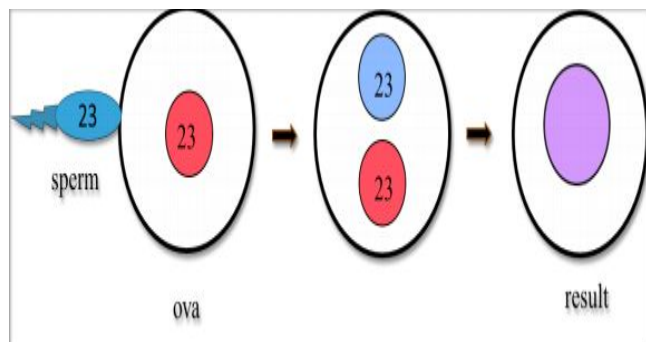


Normal Placenta



Normal Fertilization

A single sperm of 23 chromosomes fertilizes a normal egg of 23 chromosomes



Gestational Trophoblastic Disease (GTD):

- A group of related disorders in which there is an abnormal proliferation of placental trophoblasts.
- **Divided into:**
 - 1) Benign non-neoplastic lesions
 - 2) Hydatidiform moles
 - 3) Neoplastic lesions.
- The **maternal age above 40** years has 5 times more risk of trophoblastic disease compared to the mothers below 35 years.
- Most women who have had GTD can have normal pregnancies later.
- Most GTD produces the beta subunit of human chorionic gonadotropin (HCG).
- Note:
 - Serum HCG is elevated in pregnancy (normal and ectopic) but in GTD it is **markedly elevated**.
 - Also while **in normal pregnancy the HCG levels drop after 14 weeks of gestation**, in GTD the serum HCG levels continue to rise even after 14th weeks.

The GTD have been divided and classified as follows:

Benign non-neoplastic trophoblastic lesions	These are diagnosed as an incidental finding on an endometrial curettage or hysterectomy specimen.	They are: <ol style="list-style-type: none"> 1. Exaggerated placental site 2. Placental site nodule
Hydatidiform mole	Result from abnormalities in fertilization. They are essentially benign, but carry an increased risk of developing malignant choriocarcinoma.	They are: <ol style="list-style-type: none"> 1. Complete hydatidiform mole 2. Partial hydatidiform mole 3. Invasive mole/chorioadenoma destruens
Gestational trophoblastic neoplasia (GTN)	A group of tumors. They have potential for local invasion and metastases.	They are: (malignant) <ol style="list-style-type: none"> 1. Choriocarcinoma 2. Placental site trophoblastic tumor 3. Epithelioid trophoblastic tumor

Hydatidiform Mole:

- An abnormal fertilization resulting in an abnormal placenta due to **excess of paternal (from father) genes**.
- It is caused by abnormal gametogenesis and fertilization.
- The most common form of GTD; occurs in 1/1,000-2,000 pregnancies.
- 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. The **serum HCG concentration is markedly elevated**, and are rapidly increasing.

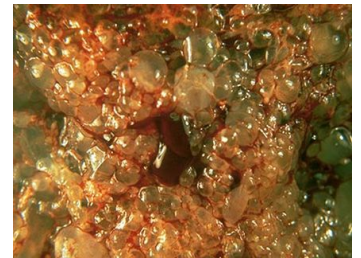
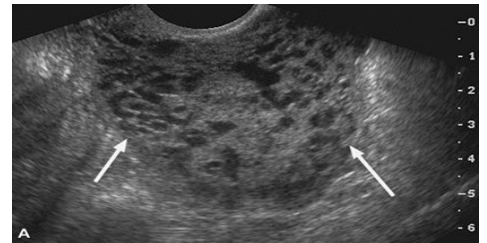
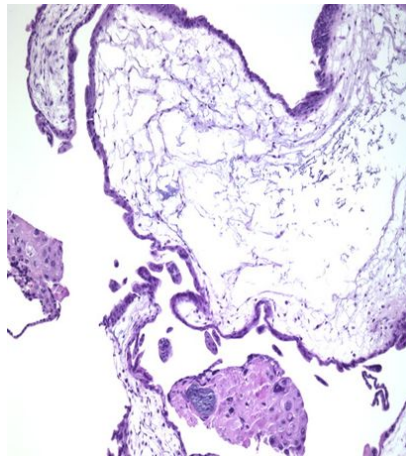
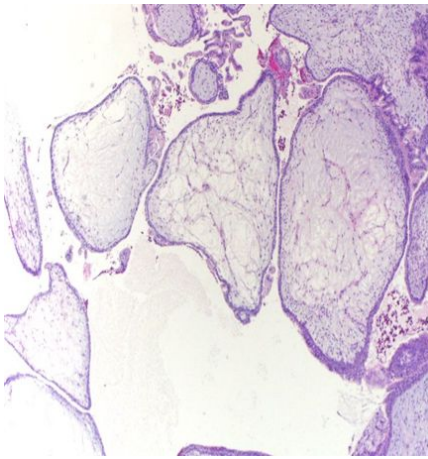
Types	<ol style="list-style-type: none">1. Complete HM2. Partial HM.
Histologically	Cystic swelling of the chorionic villi with variable trophoblastic proliferation.
Risk Factors	<ul style="list-style-type: none">● Maternal age: girls < 15 years of age and women > 40 are at higher risk.● Ethnic background: incidence higher in Asian women.● Women with a prior hydatidiform mole have a 20-fold greater risk of a subsequent molar pregnancy than the general population.

Complete HM

- Complete mole results from fertilization of an empty ovum that lacks maternal DNA → as a result all chromosomal material is 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%, **46 XY as a result of fertilization of an empty ovum by 2 sperm (dispermy)**.
- It is a genetically abnormal placenta with hyperplastic trophoblasts, without fetus or embryo.
- **Symptoms: fast rate of abdominal swelling** (due to rapid increase in uterine size) mistaken for normal pregnancy but the uterus is disproportionately large for that stage of pregnancy. In addition patient has some **vaginal bleeding, severe nausea and vomiting. HCG levels are elevated.**
- Uterus is distended and filled with swollen/large villi with prominent trophoblastic cell proliferation. **No embryo, or fetal tissue** is present. Grossly it looks like a **bunch of grapes**.

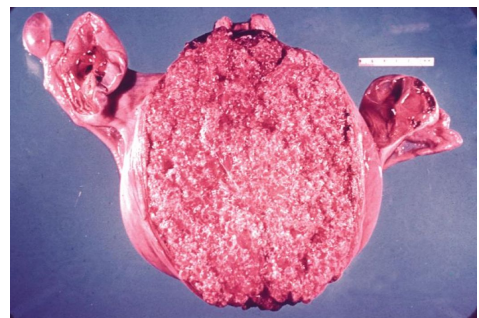
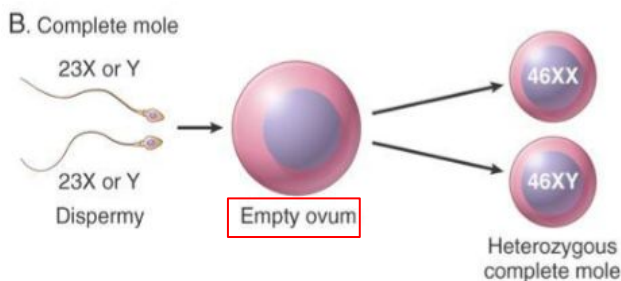
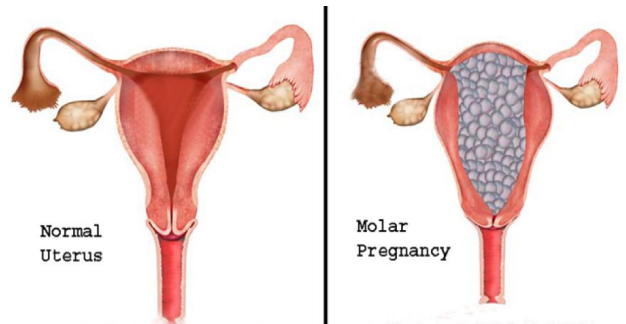
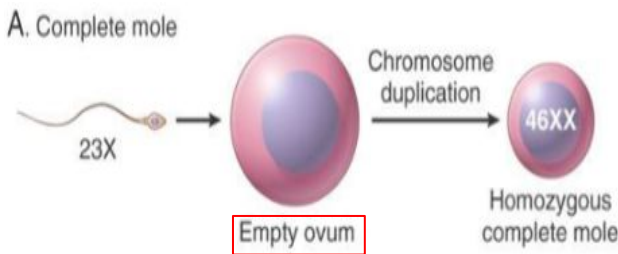
Complete HM

- **Ultrasound:** will show a “**cluster of grapes**” appearance or a “**snowstorm**” appearance, signifying an abnormal placenta.
- **Treatment:** Evacuation of uterus by curettage and sometimes chemotherapy. With appropriate therapy cure rate is very high.
- **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. (Very important)



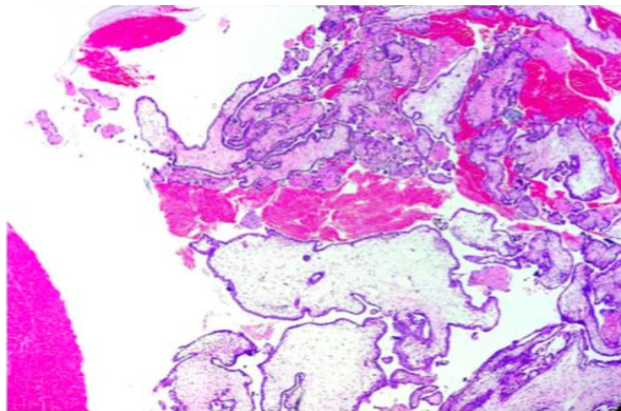
Complete mole fertilization:

- 90% of the time, a single sperm of 23 chromosomes fertilizes a egg that has lost its chromosomes. It then duplicates resulting in **46 XX** (all paternal).
- 10% of cases are **46 XY** as a result of fertilization of an empty ovum by 2 sperm (dispermy).



Partial HM

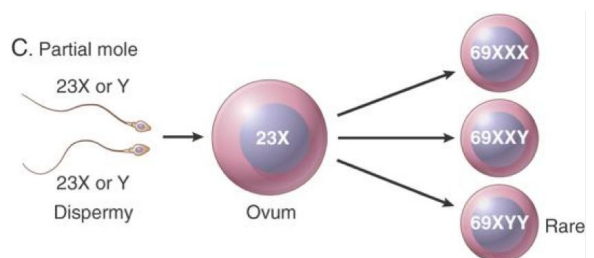
- Partial hydatidiform mole results from fertilization of a normal ovum (that has not lost its maternal chromosome) by 2 normal sperms. This results in a triploid cell having 69 chromosomes (triploidy gestation), of which one haploid set (23X) is maternal and two haploid (23+23=46) sets are paternal in origin.
- It is a genetically abnormal placenta with a resultant mixture of large and small villi with 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.
- **Rare to progress to choriocarcinoma.**
- Grossly the genetically abnormal placenta has a **mixture of large chorionic villi and normal-appearing smaller villi**.
- It makes up 15–35% of all moles.
- Uterine size usually small or appropriate for gestational age.
- **Serum HCG levels are high but not as high as complete mole.**
- Chromosomal analysis of partial moles shows 69 XXY in majority of cases (i.e. 3 haploid sets also called as **triploidy**).
- **Treatment:** Evacuation of uterus by curettage and sometimes chemotherapy. (like treatment of complete mole)
- **Prognosis:** Risk for development of choriocarcinoma very low. Follow-up is mandatory.



- Swollen enlarged edematous villi
- Two populations of villi

Partial mole fertilization:

- This results from fertilization of a normal single ovum/egg (23X) by two normal spermatozoa, each carrying 23 chromosomes, or by a single spermatozoon that has not undergone meiotic reduction and bears 46 chromosomes (the pregnancy has too much paternal DNA).
 - 58% are 69XXY (Most common)
 - 40% are 69XXX
 - 2% are 69YY

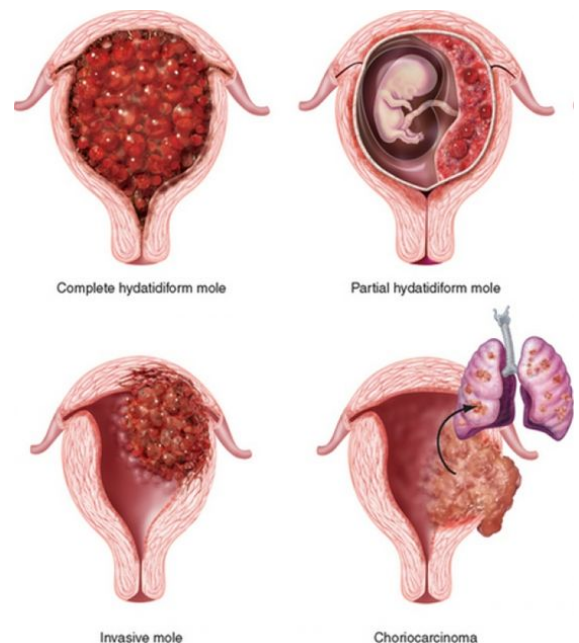


Complete mole vs Partial mole (very important)

Feature	Complete mole	Partial mole
Karyotype	Usually diploid 46XX	Usually triploidy 69XXY (most common)
Vili	All villi are hydropic; no normal villi seen	Normal villi may be present
Fetal Tissue	Not present	Usually present
Trophoblast	Marked proliferation	Mild proliferation
Serum HCG	Markedly elevated	Less elevated
Invasive mole	Occurs in about 15% of CMs	Very rare
Behavior	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 enter into the veins in the myometrium, and a times spread via the 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.
- Can cause hemorrhage and uterine perforation.

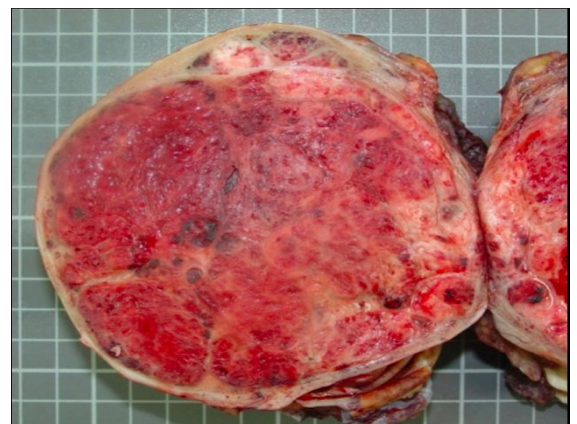
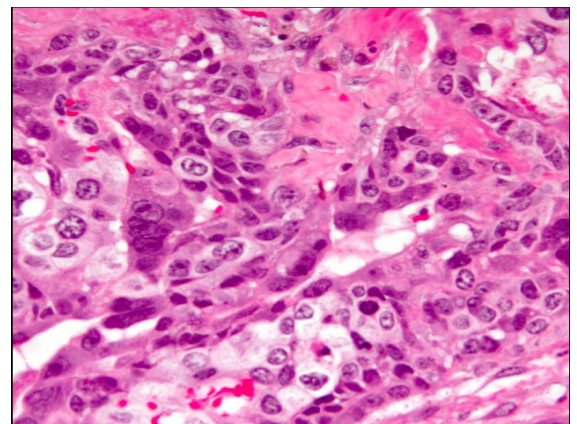


Choriocarcinoma

- Definition: **Malignant** tumor of placental tissue, composed of a proliferation of malignant cytotrophoblast and syncytiotrophoblast, **without villi formation**.
- It is an aggressive malignant neoplasm.
- It is characterized by **very high levels of serum HCG**.
- Choriocarcinomas are aneuploidic.
- It spreads early via blood to the **lungs and other organs**.
- Responds to **chemotherapy**.
- About half 50% of the choriocarcinoma are preceded by complete hydatidiform mole . Others can be preceded by partial mole (**rare**), abortion, ectopic pregnancy and occasionally normal term pregnancy.



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Pathoma Overview

GESTATIONAL PATHOLOGY

1. ECTOPIC PREGNANCY

- a. Implantation of fertilized ovum at a site other than the uterine wall; most common site is the lumen of the fallopian tube
- b. Key risk factor is scarring (e.g., secondary to pelvic inflammatory disease or endometriosis).
- c. Classic presentation is lower quadrant abdominal pain a few weeks after a missed period.
 - i. Surgical emergency; major complications are bleeding into fallopian tube (hematosalpinx) and rupture.

2. SPONTANEOUS ABORTION

- a. Miscarriage of fetus occurring before 20 weeks gestation (usually during first trimester)
 - i. Common; occurs in up to 1/4 of recognizable pregnancies
- b. Presents as vaginal bleeding, cramp-like pain, and passage of fetal tissues
- c. Most often due to chromosomal anomalies (especially trisomy 16); other causes include hypercoagulable states (e.g., antiphospholipid syndrome), congenital infection, and exposure to teratogens (especially during the first 2 weeks of embryogenesis).
 - i. Effect of teratogens generally depends on the dose, agent, and time of exposure
 1. First two weeks of gestation-spontaneous abortion
 2. Weeks 3-8-risk of organ malformation
 3. Months 3-9-risk of organ hypoplasia

3. HYDATIDIFORM MOLE

- a. Abnormal conception characterized by swollen and edematous villi with proliferation of trophoblasts
- b. Uterus expands as if a normal pregnancy is present, but the uterus is much larger and much higher than expected for date of gestation.
- c. Classically presents in the second trimester as passage of grape-like masses through the vaginal canal.
 - i. With prenatal care, moles are diagnosed by routine ultrasound in the early first trimester. Fetal heart sounds are absent, and a 'snowstorm' appearance is classically seen on ultrasound.
- d. Classified as complete or partial
- e. Treatment is dilatation and curettage.
 - i. Subsequent monitoring is important to ensure adequate mole removal and to screen for the development of choriocarcinoma.
 1. Choriocarcinoma may arise as a complication of gestation (spontaneous abortion, normal pregnancy, or hydatidiform mole) or as a spontaneous germ cell tumor.
- f. ii. Choriocarcinomas that arise from the gestational pathway respond well to chemotherapy; those that arise from the germ cell pathway do not.

MCQ

- 1) Which of the following is the ultrasound appearance of Complete Hydatidiform Mole (CHM)?
 - a) Swiss cheese appearance
 - b) Cluster of grapes appearance
 - c) Whorled appearance
 - d) Cystic appearance
- 2) What is the most common genotype for partial mole fertilization?
 - a) 69 XXY
 - b) 69 XXX
 - c) 69 XYY
 - d) 69 XO
- 3) Which of the following has a high chance of progression to choriocarcinoma?
 - a) Partial mole
 - b) Complete mole
 - c) Invasive mole
 - d) A&C
- 4) Cluster grape appearance typically presents in which of the following ?
 - a) Complete mole
 - b) Partial mole
 - c) Invasive mole
 - d) Choriocarcinoma
- 5) A 21-year-old G2, P1 woman is in the early second trimester. She has noted a small amount of vaginal bleeding for the past week and has had marked nausea and vomiting for 3 weeks. 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 in the figure. Which of the following substances is most likely to be greatly increased in her serum?
 - a) Human chorionic gonadotropin
 - b) Acetylcholinesterase
 - c) Alpha Fetoprotein
 - d) Human placental lactogen
- 6) which one of the following is a risk factor for hydatidiform mole?
 - a) 22 years old with history of smoking
 - b) 45 years old Asian female
 - c) 55 years old alcoholic male
 - d) 30 years old female with history of breast cancer

Cases From (436)

1. A 32-year-old female presented to the hospital with bloody brownish discharge. Laboratory tests revealed elevated Beta-hCG in blood and urine. Imaging showed multiple masses in the lung, vagina and liver.

Q1) Biopsy was taken, what do you expect to see?

Q2) What is the diagnosis?

2. A 17-year-old girl missed a menstrual period, and her pregnancy test is positive. A month later, she notes suprapubic pain and passing blood clots from her vagina. She passes a small amount of tissue 3 days later. Pathologic examination of this tissue shows products of conception.

Q1) Which of the following is the most likely cause for her pregnancy loss?

Answers:

A1) Anaplastic cuboidal cytotrophoblasts

A2) Choriocarcinoma

A3) Fetal Trisomy 16



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References:



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