



# TROPHOBLASTIC DISEASE

{ ومن لم يذق مرّ التعلّم ساعةً.. تجرع ذلّ الجهل طوال حياته }



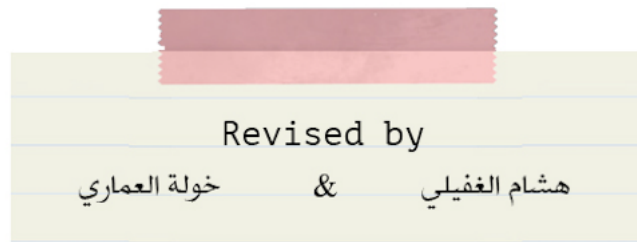
## Lecture Seven

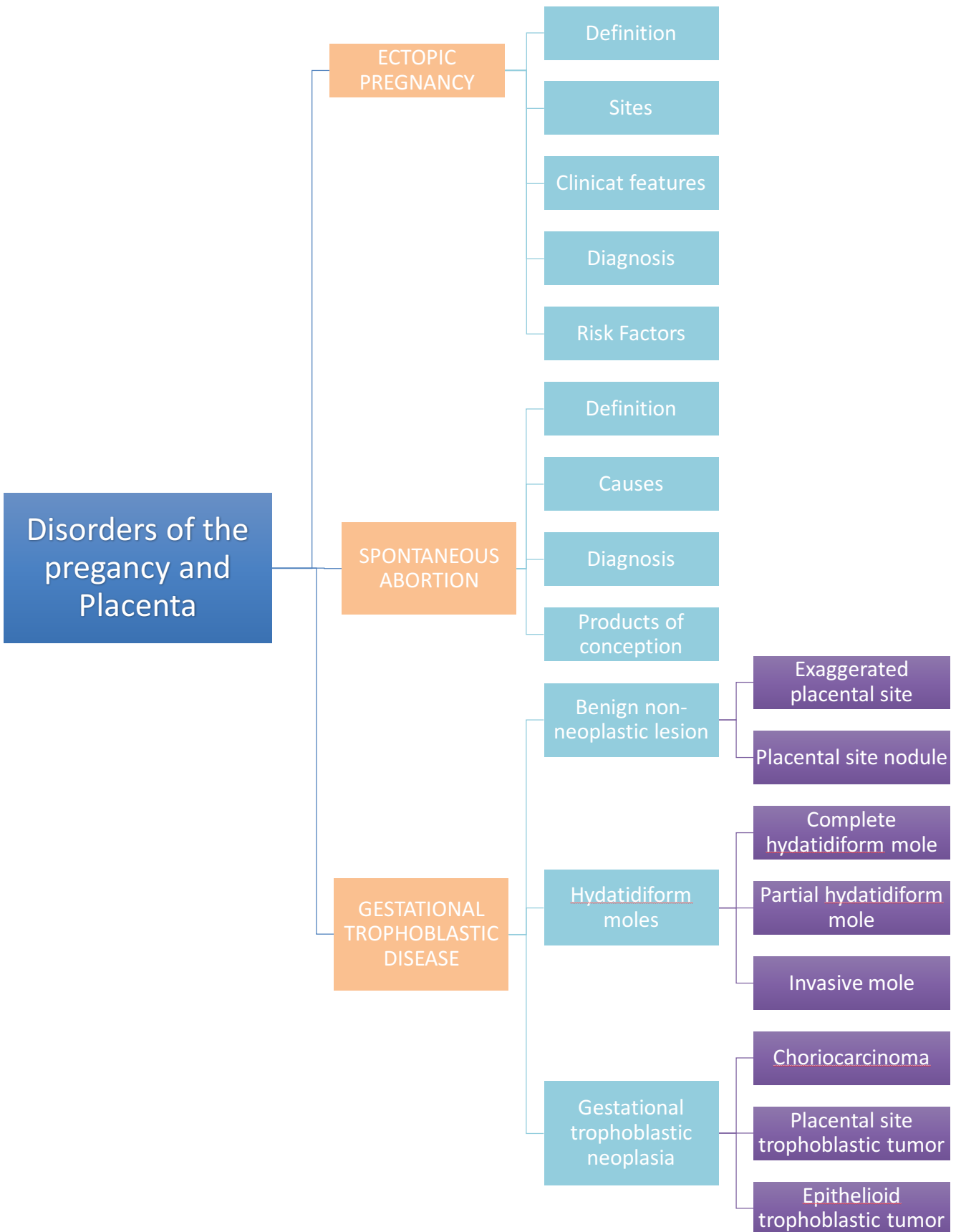
### Objectives:

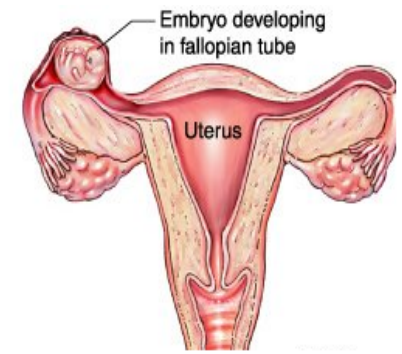
At the end of this lecture, the student should be able to:

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

References: Lecture slides & Robbins







# 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)** most common type of ectopic pregnancies.
- Other sites of pregnancy include the ovaries, abdominal cavity and uterine cervix.
  - **Ovarian pregnancies:** results when the ovum is fertilized just as the follicle ruptures (rare).
  - **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 Factors:** **NOTE:** In many tubal pregnancies, no anatomic cause is evident.

**Pelvic inflammatory disease/infections/salpingitis**

- One of the most common causes.
- The inflammation may 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.
- Organisms like **Neisseriae gonorrhoea** and **chlamydia** infect the reproductive organs.

**History of:**

- **Previous ectopic pregnancy.**
- **Multiple sexual partners** (because it has an ↑ chance of pelvic inflammatory disease → ↑ risk for ectopic pregnancy).
- **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.

**Smoking**

- May contribute to decreased tubal motility by damaging ciliated cells or it may be predisposing them to pelvic inflammatory disease (due to the impaired immunity in smokers).

**In-utero diethylstilbestrol (DES) exposure**

- Increases the risk of ectopic pregnancy due to abnormal tubal morphology.

**Others**

- Abdominal/pelvic **surgery** or **tubal ligation** surgery.
- **Intrauterine tumors and endometriosis.**
- Congenital **anomaly** of the tubes.
- **Intrauterine device users** are at higher risk of having an ectopic pregnancy.

## Clinical Features

- A woman with an ectopic tubal pregnancy may present with pelvic pain or abnormal bleeding following a period of amenorrhea<sup>1</sup>.
- The majority will present as an emergency with tubal rupture and hemorrhagic shock.
- **Tubal ectopic pregnancy:** fallopian tubes are the most common location for ectopic pregnancies and 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.** (fallopian tube)

## Diagnosis

- **Clinical:** Abdominal/pelvic ultrasound shows mass (gestational sac) within fallopian tube, plus positive HCG levels (human chorionic gonadotropin)
- **Microscopic:** Placental tissue or fetal parts.
- When they conform the diagnosis, they should immediately enter the surgery room before it leads to rupture, a lot of bleeding and pain.

## Spontaneous abortion (SAB) “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 sixth week of gestation are called **early pregnancy loss or chemical pregnancy.** In the first trimester, the most common cause is chromosomal abnormality.
- Miscarriages that occur after the sixth 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 of pregnancy.

## Diagnosis

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

<sup>1</sup> An abnormal absence of menstruation



Causes	<ul style="list-style-type: none"> <li>Most miscarriages occur during the <b>first trimester</b>.</li> <li>The cause of a miscarriage <b>cannot</b> always be determined.</li> <li>Miscarriages can occur for many reasons: genetic, uterine abnormalities, hormonal abnormalities, collagen vascular disease (e.g. SLE), reproductive tract infections, and congenital (present at birth) abnormalities of the uterus.</li> <li><b>Chromosomal abnormalities</b> of the fetus are the most common cause of early miscarriages.</li> </ul> <p><b>The causes are as follows:</b></p>				
	Chromosomal abnormalities	<ul style="list-style-type: none"> <li><b>Half</b> of the 1st trimester miscarriages have abnormal chromosomes.</li> <li>Chromosomal abnormalities also become more common with aging, and women over <b>age 35</b> have a higher rate of miscarriage than younger women.</li> <li>A pregnancy with a genetic problem has a <b>95%</b> probability of ending in miscarriage.</li> </ul>	Abnormal structural anatomy	(of the uterus) can also cause miscarriages e.g. septate or bicornuate 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.	
	Hormonal problems	<p>There is an increased risk of miscarriage with:</p> <ul style="list-style-type: none"> <li>➤ <b>Cushing's Syndrome</b>, Thyroid disease or Polycystic ovary syndrome.</li> <li>➤ <b>Diabetes</b>: good control of blood sugars during pregnancy is important. If the diabetes is not well controlled, there is an increased risk of miscarriages and also of the baby to have birth defects.</li> <li>➤ <b>Inadequate</b> function of the corpus luteum in the <b>ovary (which produces progesterone necessary for maintenance of the very early stages of pregnancy)</b> leads to progesterone deficiency which may lead to miscarriage. (remember progesterone relaxes the uterine smooth muscle contraction, so no progesterone = premature contraction and miscarriage)</li> </ul>			
	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. (the first two organisms are parasites and the rest are viruses; Congenital infections: T. gondii, Parvovirus, Rubella, herpes, CMV)	Maternal health problems	<b>Can predispose to miscarriages e.g.</b> systemic lupus erythematosus and antiphospholipid antibody syndrome (both are autoimmune diseases)	
Lifestyle	Smoking, drug use, malnutrition, excessive caffeine and exposure to radiation or toxic substances.	Maternal age	SABs (spontaneous abortions) increase after age 35 due to ovum abnormalities	Maternal trauma Others	Surgical procedures in the uterus during pregnancy e.g. amniocentesis and chorionic villus sampling. <b>(both are prenatal test to detect fetal abnormalities)</b>

**Remember:** In Normal fertilization a sperm of 23 chromosomes meets a normal egg of 23 chromosomes and form a zygote with 46 chromosomes

# Gestational Trophoblastic Disease (GTD):

A group of related disorders in which there is an abnormal proliferation of placental trophoblasts.

- **Divided into:** Benign non-neoplastic lesions, Hydatidiform moles & 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).**
- **Serum HCG** is elevated in pregnancy (normal and ectopic) but in GTD it is **markedly** elevated. However, **in normal pregnancy the HCG levels drop after 14 weeks of gestation,** but in GTD the serum HCG levels continue to rise even after 14th weeks.

## The GTD have been divided and classified as follows:

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

## 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.

### Risk Factors

- **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.

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

<sup>2</sup> Not going to be asked about it just read them.

	Complete	Partial
Results from	Fertilization of an <b>empty ovum</b> that lacks maternal DNA. Most commonly, a haploid (23X) set of paternal chromosomes duplicates to 46XX ( <b>The most common type in CM</b> ) The characteristic feature is <b>complete lack of maternal chromosomes</b> . 10% are 46XY because of dispermy.	Fertilization of a <b>normal single ovum/egg</b> (23,X) 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 <b>too much paternal DNA</b> ).
It is	A genetically abnormal placenta with hyperplastic trophoblasts, <b>without fetus or embryo</b> .	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, <b>embryo/fetal parts may be present</b> . The fetus associated with a partial mole usually <b>dies after 10 weeks' gestation</b> , and the mole is aborted shortly thereafter.
Symptoms	<ul style="list-style-type: none"> <li>- Fast rate of abdominal swelling (due to <b>rapid increase in uterine size</b>) mistaken for normal pregnancy but the uterus is disproportionately large for that stage of pregnancy.</li> <li>- Some vaginal bleeding, severe nausea and vomiting. <b>HCG levels are elevated</b>.</li> </ul>	<ul style="list-style-type: none"> <li>- It makes up <b>15–35% of all moles</b></li> <li>- <b>Uterine size usually small</b> or appropriate for gestational age</li> <li>- <b>Serum HCG levels are high but not as high as complete mole</b>.</li> </ul>
Signs	<ul style="list-style-type: none"> <li>- <b>Uterus is distended and filled with swollen/large villi</b> with prominent trophoblastic cell proliferation.</li> <li>- No embryo, or fetal tissue is present. Grossly it looks like a bunch of grapes.</li> </ul>	Grossly the genetically abnormal placenta has a mixture of large chorionic villi and normal-appearing smaller villi.
CA	Chromosomal analysis shows 46XX karyotype and all the chromosomes come from the male/paternal side i.e. it is an <b>androgenetic pregnancy with no maternal DNA</b> .	<ul style="list-style-type: none"> <li>• <b>Shows 69XXY in 58%</b> (<b>The most common type in PM</b>) (i.e. 3 haploid sets also called as <b>triploidy</b>)</li> <li>• 40% are 69XXX &amp; 2% are 69XYY.</li> </ul>
Fertilization	90% of the time, a single sperm of 23 chromosomes fertilizes a egg that has lost its chromosomes. It then duplicates resulting in <b>46XX</b> (all paternal)	Have <b>69 chromosomes</b> (triploidy gestation), of which one haploid set (23,X) is maternal and two haploid (23,X+23X=46X) sets are paternal in origin.
US	Will show a <b>“cluster of grapes”</b> appearance or a <b>“snowstorm”</b> appearance, signifying an abnormal placenta.	-
Tx	<b>Evacuation</b> of uterus by <b>curettage</b> and sometimes <b>chemotherapy</b> . With appropriate therapy <b>cure rate is very high</b> .	<b>Evacuation</b> of uterus by <b>curettage</b> and sometimes <b>chemotherapy</b>
Complications	<ul style="list-style-type: none"> <li>- Uterine hemorrhage, perforation.</li> <li>- Trophoblastic embolism, and infection.</li> <li>- Few patients develop an invasive mole 10%.</li> <li>- The most important complication is the <b>development of choriocarcinoma</b>, which occurs in <b>about 2%</b> of patients after the mole has been evacuated.</li> </ul>	It almost <b>never evolves into choriocarcinoma</b> . <b>Prognosis:</b> Risk for development of choriocarcinoma very low. <b>Follow-up is mandatory</b> .

FEATURE	CM	PM
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 10-15% of CMs	Very rare
Behavior	2% progress to choriocarcinoma	Very rarely progress to choriocarcinoma

### ➤ Invasive Mole:

- When the villi of a hydatidiform mole extends/infiltrates into the myometrium of the uterus but do not have the aggressive metastatic potential of a choriocarcinoma.
- The mole sometimes enters into the veins in the myometrium (so difficult to remove), and at times spreads via the vascular channels (may embolize) to distant sites, mostly the lungs (note: death from such spread is unusual). (& embolism regresses spontaneously)
- It occurs in about **15% of complete** moles and rarely in partial mole.
- Can cause hemorrhage (life-threatening) and uterine perforation.<sup>3</sup>
- After removal, if serum  $\beta$ -hCG remains elevated, further treatment is required.
- Fortunately, in most cases cure is possible with chemotherapy.

## Choriocarcinoma:

**Malignant tumor** of placental tissue, composed of a proliferation of malignant anaplastic cuboidal cytotrophoblast and syncytiotrophoblast, **without villi formation**.

- An aggressive malignant neoplasm characterized by **very high levels of serum HCG**.
- **Aneuploidic**, spreads early via blood to the 50% lungs and vagina (30% to 40%), brain, liver, or kidneys. Lymphatic invasion is uncommon.
- Responds well to chemotherapy (Nearly 100% of affected patients are cured) but choriocarcinoma that affects the gonads' prognosis is poor why? Because it is lacking paternal antigens which are found on placental choriocarcinomas.
- About half the choriocarcinoma are preceded by **complete hydatidiform** mole. Others are preceded by a partial mole (rare), 25% from abortion, ectopic pregnancy and **occasionally normal term pregnancy**.



<sup>3</sup> If it was very bad.

© 2006 Elsevier Inc.



# Now Check Your Understanding!

## MCQs: (First 3 are from 434)

- 1. 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
- 2. Sarah is a 20-year-old obese woman who had a miscarriage. She noticed stretch marks on the breasts, arms, abdomen, and thighs. Also experiences fatigue, muscle weakness and increased thirst. She expressed her concerns with noticing excessive growth of facial or body hair. Lab tests, show hypertension, and increased blood glucose. What is the most likely cause of her miscarriage?**
  - A. Chromosomal abnormalities
  - B. Diabetes
  - C. Cushing syndrome
  - D. Inadequate function of the corpus luteum in the ovary

Note: symptoms were not mentioned in this team work. However, taken in the endocrine block.

- 3. A 21-year-old woman presents to her gynecologist with a 3-day history of vaginal bleeding. Evacuation of the uterus by suction curettage reveals grapelike clusters. Lab finding show diffuse circumferential proliferation around hydropic villi, with most of the villi being hydropic. Which of the following is most likely the cause?**
  - A. Normal ovum fertilized by two sperms
  - B. Empty ovum fertilized by two sperm
  - C. Normal ovum fertilized by a sperm
  - D. Empty ovum fertilized by a sperm

Help: with the grapelike clusters, diagnosis for Hydatidiform Mole was made. Then lab findings show that the patient has Partial Hydatidiform Mole. which genetically, is due to normal ovum fertilized by two sperms.

- 4. What is the most common site of ectopic pregnancy?**
  - A. Ovaries
  - B. Fallopian Tube
  - C. Uterus
  - D. Vagina

5. **Most miscarriages occur during which of the gestational trimesters?**
- A. 1<sup>st</sup> trimester.
  - B. 2<sup>nd</sup> trimester.
  - C. 3<sup>rd</sup> trimester.
  - D. 4<sup>th</sup> trimester.
6. **Which one of the following cannot be a site of ectopic pregnancy?**
- A. Fallopian tubes
  - B. Abdominal cavity.
  - C. Vagina.
7. **A 45-year-old pregnant woman presents with vaginal bleeding, severe nausea and vomiting. The ultrasound show "cluster of grapes" appearance and signifying an abnormal placenta, Chromosomal analysis shows 46XX karyotype. What is the most likely diagnosis?**
- A. Chorioadenoma.
  - B. Complete Hydatidiform mole.
  - C. Neoplastic lesions.
  - D. Partial hydatidiform mole
8. **Which one of the following does not cause spontaneous abortion?**
- A. Cushing syndrome.
  - B. Nephrotic syndrome.
  - C. Smoking.
  - D. Systemic lupus erythematosus.
9. **Which sentence best describes the pathogenesis behind ectopic pregnancy?**
- A. The cilia of the fallopian tube catch the ovum to be fertilized and implanted there.
  - B. Fibrous tissue in the fallopian tube retard the passage ovum.
  - C. Immovable fertilized ovum stays in fallopian tube to be fertilized there.
  - D. Any condition block the passage of the ovum toward uterus lead to ectopic implant.

Answers:

1: B    2: C    3: A    4: B    5: A  
6: C    7: B    8: B    9: D





Thanks for checking our work! Good Luck.

Done by:

نوف التويجري & عمر آل سليمان

عبدالله الطشان

نورة الخراز

عبدالعزیز الشعلان

محمد الدغیثر

عبدالله العلیوی

{ قال صلی الله علیه وسلم: من سلك طريقًا يلتمس فيه علمًا سهل الله له به طريقًا إلى الجنة }  
{

