

## DISORDER OF PREGNANCY AND PLACENTA



#### **Objectives:**

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

**Important note:** Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all or our work: <u>Pathology Edit.</u>

Grey = Extra Red = Important

# 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). (most common location)
- Other sites include the ovaries, abdominal cavity and uterine cervix.
- ★ **Ovarian pregnancies** probably result from rare instances in which the <u>ovum is fertilized just as the follicle ruptures.</u>
- ★ Gestation within the **abdominal cavity** occurs when the fertilized egg drops out of the fimbriated end of the oviduct and implants on the peritoneum.

#### **Clinical features**

- Pelvic pain. (because fallopian tube cannot accommodate enlargement)
- Abnormal bleeding following a period of amenorrhoea.
- The majority will present as: emergency with lower quadrant abdominal pain, bleeding into fallopian tube (hematosalpinx), tubal rupture and hemorrhagic shock.

#### Diagnosis: (two ways)

#### • Clinical:

- 1. Abdominal/pelvic ultrasound shows mass (gestational sac) within fallopian tube
- 2. Positive hCG levels
- Microscopic: of Placental tissue or fetal parts.

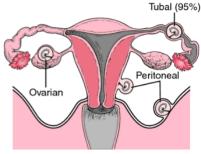


### **Risk factors for ectopic pregnancy:**

Ectopic pregnancies & any factor that retards passage of the ovum through the tubes  $\rightarrow$  tubal ectopic pregnancy.

- In about half of the cases due to chronic inflammation → damage ciliary activity, tubal obstruction, pelvic adhesions with scarring in the oviduct and distortion of the fallopian tubes. Such as salpingitis, Pelvic inflammatory disease, pelvic infections caused by Neisseriae gonorrhea and chlamydia five times increased the risk of ectopic pregnancy
- 2. Abdominal/pelvic surgery or tubal ligation surgery.
- 3. Intrauterine tumors and endometriosis.
- 4. Smoking by two ways : A-damaging ciliated cells  $\rightarrow$  decreased tubal motility
- B--pelvic inflammatory disease  $\rightarrow$  due to the impaired immunity 5. Congenital anomaly of the tubes.
- **6.** In-utero diethylstilbestrol (DES)  $\rightarrow$  abnormal tubal morphology. So increases the risk of ectopic pregnancy
- 7. History of previous ectopic pregnancy
- 8. History of multiple sexual partners  $\rightarrow$  pelvic inflammatory disease and therefore are high risk for ectopic pregnancy.
- 9. Intrauterine device users
- **10.** History of infertility due to 1- the underlying infertility related issues 2-fertility drugs and treatments. In vitro fertilization has been associated with an increased risk of ectopic pregnancy including cervical pregnancies

NOTE: please note that in many tubal pregnancies, no anatomic cause is evident



## **SPONTANEOUS ABORTION/ Miscarriage**

- It is the spontaneous end of a pregnancy at a stage where the embryo or fetus is <u>incapable</u> <u>of surviving</u>.
- Miscarriages that occur before the sixth week of gestation are called *early pregnancy loss* or *chemical pregnancy*.
- 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 (1st trimester) of pregnancy.



#### **Causes of SAB/Miscarriage:**

1. Chromosomal abnormalities	<ul> <li>The most common cause of early miscarriages</li> <li>Half of the 1st trimester miscarriages have abnormal chromosomes.</li> <li>A pregnancy with a genetic problem has a 95% probability of ending in miscarriage. (especially trisomy 16)</li> <li>Chromosomal abnormalities become more common with aging that's why women over age 35 have a higher rate of miscarriage than younger women.</li> <li>Only 5% is the survival rate.</li> <li>Ex. Down syndrome</li> </ul>				
2. Hormonal problems	<ul> <li>Cushing's Syndrome</li> <li>Thyroid disease</li> <li>Polycystic ovary syndrome (PCOS).</li> <li>Diabetes: good control of blood sugars during pregnancy is important. uncontrolled diabetes increase risk of miscarriages and also of the baby to have birth defects. Also the controlled DM can increase the risk.</li> <li>Inadequate function of the corpus luteum luteum in the ovary (which produces progesterone necessary for maintenance of the very early stages of pregnancy) → leads to progesterone deficiency → miscarriage.</li> </ul>				
3. Infections	<ul> <li>Congenital infection (Toxoplasma gondii, parvovirus B19, rubella, herpes simplex, cytomegalovirus)</li> <li>Listeria monocytogenes</li> <li>lymphocytic choriomeningitis virus</li> </ul>				
4. Maternal health problems	<b>e.g.</b> systemic lupus erythematosus and antiphospholipid antibody syndrome (a hypercoagulable state)				
5. Lifestyle	<ul> <li>Smoking</li> <li>Drug use</li> <li>Malnutrition</li> <li>Excessive caffeine</li> <li>Exposure to radiation</li> <li>Toxic substances</li> </ul>				
6. Maternal age	SABs increase after age 35 due to ovum abnormalities				
7. Maternal trauma	-				
8 Abnormal structural anatomy of the uterus	<ul> <li>Such as septate or bicornuate uterus affect placental attachment and growth. → embryo implanting on the septum → increased risk of miscarriage.</li> <li>uterine fibroids (due to previous infection or inflammation → affects embryo implantation and blood supply, → miscarriage</li> </ul>				
9. Others	surgical procedures in the uterus during pregnancy e.g amniocentesis and chorionic villus sampling.				
10. Exposure to teratogens	Especially during the first 2 weeks of embryogenesis.				

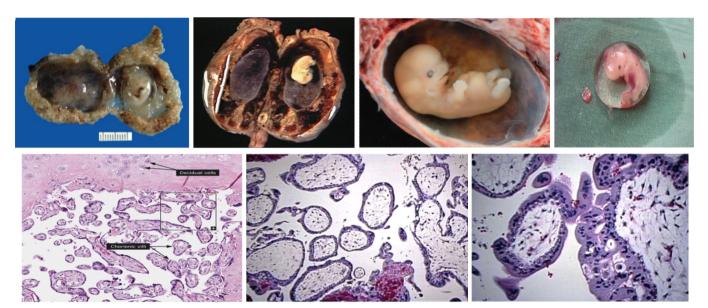
#### **Diagnosis**:

A miscarriage can be confirmed via:

- Ultrasound
- **Microscopic examination** of the passed tissue for the products of conception shows chorionic villous, trophoblasts with they line the villi cytotrophoblast and syncytiotrophoblast, fetal parts, and background gestational changes in the endometrium.
- The contents of the miscarriage depends on the weeks, 5 to 6 weeks  $\rightarrow$  Masses , 10 weeks and more  $\rightarrow$  Placental tissues
- **Genetic tests** may also be performed to look for chromosomal anomalies.

#### **Clinical features**

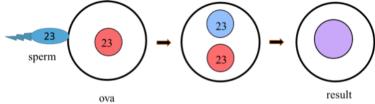
Presents as vaginal bleeding, cramp-like pain, and passage of fetal tissues.



## **Gestational Trophoblastic Disease**



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



# **GTD**: Is a group of related disorders in which there is abnormal proliferation of placental trophoblasts.

- The maternal age above 40 years has a 5 times more risk of trophoblastic disease compared to the mothers below 35 years.
- Most women who have had gestational trophoblastic disease can have normal pregnancies later.
- Most GTD produces the beta subunit of human chorionic gonadotropin (HCG).

#### NOTE:

- 1. Serum HCG is also elevated in Pregnancy (normal and ectopic) but in GTD it is markedly elevated. ( uterus will larger than normal as well.)
- 2. 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.

1. Benign non-neoplastic trophoblastic lesions	2. Hydatidiform mole	3. Gestational trophoblastic neoplasia (GTN)
These are diagnosed as an incidental finding on an endometrial curettage or hysterectomy specimen.	Result from abnormalities in fertilization. They are essentially benign, but carry an increased risk of developing malignant choriocarcinoma.	Are a group of tumors. They have potential for local invasion and metastases.
<ul> <li>They are:</li> <li>● Exaggerated placental site</li> <li>● Placental site nodule</li> </ul>	<ul> <li>They are:</li> <li>Complete hydatidiform mole</li> <li>Partial hydatidiform mole</li> <li>Invasive mole/chorioadenoma destruens</li> </ul>	<ul> <li>They are:</li> <li>Choriocarcinoma</li> <li>Placental site trophoblastic tumor</li> <li>Epithelioid trophoblastic tumor</li> </ul>

#### **Divided into:** (dr.Memorize the names and focus on choriocarcinoma and hydatidiform mole only)

## Hydatidiform Mole.

The underlying idea here is that instead of growing a baby you grow abnormal placental tissue.

- It is an <u>abnormal fertilization resulting in an abnormal placenta</u> due to 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.
- The serum HCG concentration is markedly elevated, and are rapidly increasing.



#### **Risk factors:**

- Maternal age: girls younger than 15 years of age and women over 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

## **Complete HM**

 Complete mole results from fertilization of an empty ovum that lacks maternal DNA. Most commonly, a haploid (23X) set of paternal chromosomes duplicates to 46XX. The characteristic feature is complete lack of maternal chromosomes.



- of maternal chromosomes.
   Chromosomal analysis shows 46XX karyotype and all the chromosomes come from the male/paternal side i.e. it is an androgenetic pregnancy with no maternal DNA.
   It is a genetically abnormal placenta with hyperplastic trophoblasts without
- It is a genetically abnormal placenta with hyperplastic trophoblasts, <u>without</u> <u>fetus or embryo.</u>

(All of the chorionic villi are neoplastic.)

★ Grossly it looks like a bunch of grapes.

### Signs & Symptoms:

- 1. **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.
- 2. In addition patient has some vaginal bleeding,
- 3. Severe nausea and vomiting. (hyperemesis gravidarum; 8%)
- 4. HCG levels are elevated.
- 5. Preeclampsia<sup>1</sup> is present in 1% of patients.
- 6. Bilateral theca lutein cysts (15%).

<sup>&</sup>lt;sup>1</sup> Preeclampsia is a condition in pregnancy characterized by high blood pressure, sometimes with fluid retention and proteinuria.

**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. Follow patient with beta-hCG levels Should go down to zero.



#### **Complications:**

1. Uterine hemorrhage	
2. Uterine perforation	

3. Trophoblastic embolism,

4.Infection.5.Invasive mole(Few patients develop it)

6.Development of choriocarcinoma. which occurs in about 2% of patients after the mole has been evacuated.

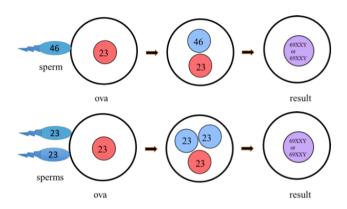
### Partial Mole (PM) 15–35% of all moles

This results from fertilization of a normal single ovum/egg (23,X) by two normal spermatozoa,Partial hydatidiform moles have 69 chromosomes (triploidy gestation).

Which:

1. One haploid set (23X) is maternal

2. Two haploid (23X+23X=46X) sets are paternal in origin.



- ★ 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).
- ★ Chromosomal analysis of partial moles shows 69XXY (i.e. 3 haploid sets also called as triploidy).
- It is a genetically abnormal placenta with a resultant *mixture of large and normal-appearing smaller villi with slight hyperplasia of the trophoblasts,* filling the uterus. In contrast to a complete mole, embryo/fetal parts may be present(because there is maternal chromosomes). The fetus associated with a partial mole usually dies after 10 weeks' gestation, and the mole is aborted shortly thereafter.
- It almost <u>never evolves into choriocarcinoma.</u>

#### Signs & Symptoms:

- Uterine size usually small or appropriate for gestational age.
- Serum HCG levels are high but not as high as complete mole.
  - Incomplete or missed abortion (90%).
  - Vaginal bleeding (75%).
  - Theca lutein cysts and hyperemesis gravidarum extremely rare.

#### Treatment : Evacuation of uterus by curettage and sometimes chemotherapy.

**Prognosis:** Risk for development of choriocarcinoma very low. **Follow-up is mandatory.** 

	PARTIAL MOLE	COMPLETE MOLE	
Genetics	Normal ovum fertilized by two sperms (or one sperm that duplicates chromosomes); 69 XXY chromosomes	Empty ovum fertilized by two sperm (or one sperm that duplicates chromosomes); 46 XX chromosomes	
Karyotype	Usually diploid 46XX	Usually triploidy 69XXY (most common)	
Fetal tissue	Not present Usually present		
Trophoblasts	Marked proliferation	Mild proliferation	
Behavior	2% progress to choriocarcinoma       Very rarely progress to choriocarcinoma		
Villi	All villi are hydropic; no normal villi seen	Normal villi may be present	
Serum HCG	Markedly elevated Less elevated		
Invasive mole	Occurs in about 15% of CMs	Very rare	

### 2. 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).

\*Patient might present with respiratory symptoms, then you might find placental tissue in the lungs.

- It occurs in about 15% of complete moles and rarely in partial mole.
- Can cause hemorrhage and uterine perforation.

## 3. Choriocarcinoma

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<sup>2</sup>.
- It spreads early via blood to the lungs and other organs (vagina, liver, brain)
   O Lesions are hemorrhagic.

<sup>&</sup>lt;sup>2</sup> Having a chromosome number that is not an exact multiple of the usually haploid number — compare euploidy ex: Down syndrome Karyotype.

#### **Risk factors:**

- 1. Complete mole (50% of cases), Partial Rare.
- 2. Spontaneous abortion (25% of cases).
- 3. Full term pregnancy (22% of cases).
- 4. Ectopic pregnancy (3% of cases).
- Excellent response to chemotherapy (methotrexate)
  - O Low mortality rate.
  - **O** Good response does not apply to non–gestationally derived choriocarcinomas (e.g, those that occur in the male testis).
  - O Excellent prognosis.

## Summary.

Ectopic Pregnancy (1% of all pregnancies)					
Definition	implantation of a fertilized ovum in any site other than the endometrium of the uterine cavity				
Clinical features		- pelvic pain or abnormal bleeding - The majority will present as an emergency with tubal rupture and hemorrhagic shock.			
Diagnosis	- Clinical: abdominal/pelvic ultrasound shows mass (gestational sac) within fallopian tube & positive hCG levels - Microscopic: placental tissue or fetal parts				
risk factors	Tubal ectopic pregnancy (90% Ectopic Pregnancy)	<ol> <li>Pelvic inflammatory disease/infections/salpingitis</li> <li>Abdominal/pelvic surgery or tubal ligation surgery.</li> <li>Intrauterine tumors and endometriosis.</li> <li>Smoking</li> <li>Congenital anomaly of the tubes.</li> <li>diethylstilbestrol (DES) exposure</li> <li>Intrauterine device users are at higher risk of having an ectopic pregnancy should</li> <li>History of : - previous ectopic pregnancy         <ul> <li>multiple sexual partners</li> <li>infertility</li> </ul> </li> <li>NOTE: in many tubal pregnancies, no anatomic cause is evident.</li> </ol>			
	Ovarian pregnancies	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.			

Spontaneous Abortion (miscarriage) (10-25% of all pregnancies)					
Definition	<b>Finition</b> It is the spontaneous end of a pregnancy at a stage where the embryo or fetus is incapable of surviving. (Most miscarriages occur during the 1 <sup>st</sup> trimester)				
types	- before the sixth week of gestation à early pregnancy loss or chemical pregnancy. - after the sixth week of gestation à clinical spontaneous abortion.				
Causes	<ul> <li>1. Chromosomal abnormalities: <ul> <li>50% of the 1st trimester miscarriages</li> <li>with aging (over age 35 &gt; younger women)</li> </ul> </li> <li>2. Hormonal problems: <ul> <li>Cushing's Syndrome</li> </ul> </li> </ul>				

	<ul> <li>Thyroid disease</li> <li>Polycystic ovary syndrome (PCOS).</li> <li>Diabetes</li> <li>Inadequate function of the corpus luteum à progeterone deficiency</li> <li><b>3. Infections:</b> Listeria monocytogenes, Toxoplasma gondii, parvovirus B19, rubella, herpes simplex, cytomegalovirus and lymphocytic choriomeningitis virus</li> <li><b>4. Maternal health problems:</b> e.g. SLE and antiphospholipid antibody syndrome</li> <li><b>5. Lifestyle:</b> smoking, drugs, malnutrition, caffeine and radiation or toxic substances</li> <li><b>6. Maternal age:</b> after age 35</li> <li><b>7. Maternal trauma</b></li> <li><b>8. Abnormal structural anatomy</b>, e.g. : septate or bicornate uterus &amp; uterine fibroids</li> <li><b>9. Others:</b> surgical procedures</li> </ul>
Diagnosis	oducts of conception.s : to look for chromosomal anomalies.

GESTATIONAL TROPHOBLASTIC DISEASE					
Definition	a group of related disorders in which there is abnormal proliferation of placental trophoblasts.				
classification	n Benign non-neoplastic Hydatidiform mole Gestational trophobl trophoblastic lesions (GTN		Gestational trophoblastic neoplasia (GTN		
	- incidental finding 1. Exaggerated placental site 2. Placental site nodule	- abnormalities in fertilization. - essentially benign, but carry an increased risk of developing malignant choriocarcinoma.	- They have potential for local invasion and metastases 1. Choriocarcinoma 2. Placental site trophoblastic tumor 3. Epithelioid trophoblastic tumor		

Hydatidiform mole					
Classification	Complete hydatidiform mole	Partial hydatidiform mole (15–35% of all moles)	Invasive mole/chorioade noma destruens	Choriocarcinoma	
Definition	fertilization of an empty ovum that lacks maternal DNA.	fertilization of a normal single ovum/egg (23,X) by two normal spermatozoa (23 chromosomes) , or by a single spermatozoon (46 chromosomes)	<ul> <li>myometrium</li> <li>infiltratration</li> <li>spread to</li> <li>distant sites,</li> <li>mostly the lungs</li> <li>It occurs in</li> <li>about 15% of</li> <li>complete moles</li> <li>and rarely in</li> <li>partial mole.</li> </ul>	<ul> <li>aggressive Malignant tumor of placental tissue</li> <li>It spreads early via blood to the lungs and other organs.</li> <li>50% preceded by complete hydatidiform mole .</li> </ul>	
Symptoms	<ul> <li>uterus size is larger than expected for the stage of pregnancy.</li> <li>vaginal bleeding</li> <li>severe nausea and vomiting.</li> </ul>	Uterine size usually small or appropriate for gestational age			
Chromosomal analysis	46XX karyotype (androgenetic pregnancy)	69 XXY chromosomes (triploidy gestation)		aneuploidic.	
Ultrasound	"cluster of grapes" appearance or a				

	"snowstorm" appearance			
Villi	All villi are hydropic; no normal villi seen	Normal villi may be present		no villi formation
Fetal tissue	Not present	Usually present		
Trophoblasts	Marked proliferation	Mild proliferation		proliferation of malignant cytotrophoblast & syncytiotrophoblast
Serum HCG	Markedly elevated	Less elevated		very high
Treatment	Evacuation of uterus by curettage and sometimes chemotherapy			Responds well to chemotherapy
Complications	<ul> <li>uterine hemorrhage,</li> <li>uterine perforation,</li> <li>trophoblastic</li> <li>embolism,</li> <li>infection.</li> <li>invasive mole.</li> <li>choriocarcinoma</li> <li>(2%)</li> </ul>	Risk for development of choriocarcinoma very low. Follow-up is mandatory.	hemorrhage and uterine perforation	

# MCQ's.

Q1) 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

Help: Clinical feat of bleeding, and the location of the enlargement, exam might include + hCG levels

**Q2)** 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.

**Q3)** 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.

#### Q4) Answer the following questions:

- A) most common form of gestational trophoblastic disease?
- B) Complete mole results from fertilization of an empty ovum that lacks maternal DNA. Most commonly due to?
- C) What is the most important complication for complete hydatidiform mole?
- D) What is the most common location for ectopic pregnancies?
- E) When do most miscarriages occur?
- F) What is the most common cause of early miscarriages?
- G) When is Fetal tissue present complete or partial hydatidiform mole?

#### H) What is the most common cause of ectopic pregnancy (mentioned in curriculum)?

A) Hydatidiform Mole, B)haploid (23X) set of paternal chromosomes duplicates to 46XX,

C)the development of choriocarcinoma,E)during the first 13 weeks of pregnancy.G) partial hydatidiform mole

D)fallopian tube, F)Chromosomal abnormalities H)Pelvic inflammatory disease

#### Q5) Mention two

1) Maternal Hormonal problems that can predispose to a miscarriage (other than cushing S)? Thyroid disease

Polycystic ovary syndrome

2) Maternal health problems that can predispose to a miscarriage? systemic lupus erythematosus

antiphospholipid antibody syndrome

## Answers: 1)B, 2)C, 3)A, 4)N/A, 5)N/A



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