Transplacental Infections

Lecture objectives

- Recognize the different types of infant infections.
- Know major transplacentally transmitted pathogens causing congenital infections .
- (Toxoplasma , TP ,ParvoV , VZV, Rubella V & CMV.)
  - Describe their structures.
  - Know their major epidemiology features.
  - Describe clinical manifestations of their congenital infections.
  - Illustrate different laboratory diagnosis of maternal and congenital infections
  - know their treatment and preventive measures.

Color index

- Important
- Doctors' note
- Extra
- Boys' slides
- Girls' slides

EDITING FILE

Reviewed by Razan AlRabah & Ibrahim AlBakhiti

MICROBIOLOGY TEAM 438

MED438 KING SAUD UNIVERSITY

Introduction

Terminology & Routes of transmission		
Classification	**Timing of events**	**Mechanisms**
Congenital	**Intra-uterine** (In utero)	• Transplacental
Perinatal[1]	**Intra-partum** (During labour and delivery)	• Exposure to genital secretions and blood
Neonatal[1]	**Post-partum** (After birth)	• Direct contact • Breastfeeding • Nosocomial

Congenital infections

- Mostly due to viruses.
- Previously known as (**TORCH**) infections:
  - **T**= **T**oxoplasma gondii
  - **O**= **O**ther e.g. (Treponema pallidum[2], parvovirus &VZV),
  - **R**= **R**ubella virus
  - **C**= **C**MV
  - **H**= **H**erpes (**H**epatitis & **H**IV)[6],

Risk of IUI & fetal damage depends on:

- **Type of Organism (Teratogenicity)**
- **Type of maternal Infection (Primary[3] ,recurrent[4])**
- **Time during pregnancy (1st[5],2nd,3rd Trimester)**

Primary maternal infection in the first half of pregnancy poses the greatest risk to the fetus.

1- e.g. Group B streptococcus infections
2- Causes syphilis
3- Initial acquisition of virus during pregnancy. **(Higher risk)** why? Because in recurrent infections there will be specific antibodies from the previous exposure which can cross the placenta and protect the fetus.This is not seen in primary infection thus making it higher risk.
4- In women who are already seropositive., reactivation of old infection. **(Lower risk)**
5- 1st trimester has higher risk for fetal damage compared to 2nd,3rd trimesters.why? Because during 1st trimester there is intensive cell division and organ development so any disturbances results in anomalies and malformations.
6- Mainly herpes simplex virus type 1 ,hepatitis B&C and we may include human papillomavirus(viruses that start with H are mainly transmitted perinatally and cause perinatal infections)

Congenital infections cont.

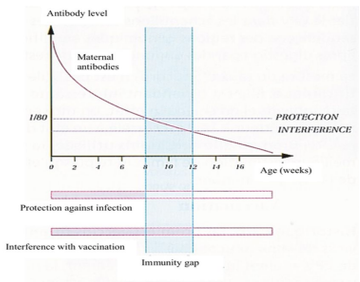
Common features of congenital infections:

- **Intrauterine growth retardation(IUGR)**
- **Microcephaly** or hydrocephalus
- Hepatosplenomegaly(HSM)
- Thrombocytopenia may result in rash
- There is also certain organ damage (eye ,ear and the heart)

NOTE: Majority of Congenital infections are asymptomatic at birth however **some** develop mental retardation and hearing loss later in life. Preventative and therapeutic measures are possible for some of the agents

Neonatal serological Diagnosis:

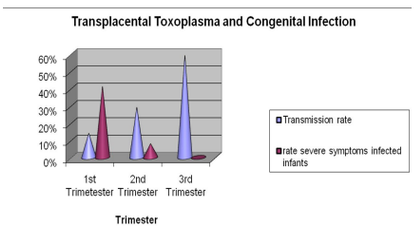
- IgM antibody.[1]
- Absence of fetal IgM at birth doesn't exclude infection.
- Persistence of specific IgG antibody > 12 months of age.[2]



1- Toxoplasmosis

Causative organism: Toxoplasma gondii

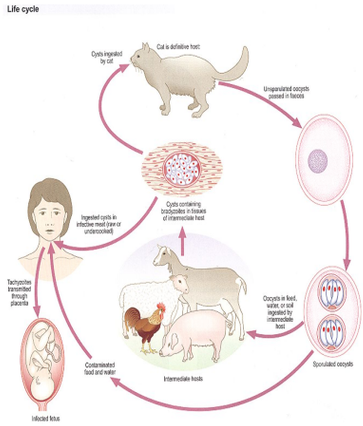
- Obligate intracellular parasite.
- Definitive host: Cats



Epidemiology:

- Most cases are due to primary maternal infection.
- Rarely, reactivation of a latent infection in immunocompromised pregnant woman
- The rate of **transmission** is the highest in the **3rd trimester**
- Fetal **death** higher with infection in **1st trimester**

Life cycle is Important

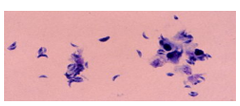
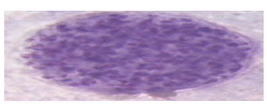


Life cycle:

Transmission:

- Ingestion of **oocytes**: **cat feces contaminate fingers, soil, water**.
- Ingestion of **cysts** in **undercooked meats**
- **Blood transfusion** and **organ transplant**
- Vertical transmission: from mother to fetus (transplacental)[3]

Morphology

Oocysts	Tachyzoites[4]  Bradyzoites[4]
• Shed in **cat feces** 	• Rapidly dividing forms • **Acute phase** • Can pass through placenta. 
	• Slowly dividing forms • **Chronic phase** 

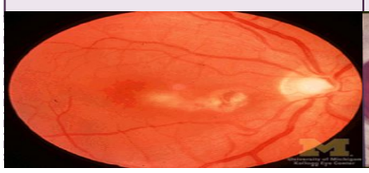
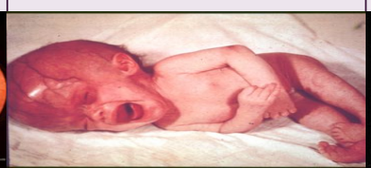
1- If you do serology for a neonate and find + IgM it indicates that the fetus has experienced an infection.
2- If you do serology for a neonate and find + IgG this doesn't necessarily indicate a previous infection, because it's probably Maternal IgG , IgG can cross the placenta unlike other Abs, so we do the test again after 12 months (Maternal IgG will be gone), if positive this indicates that the fetus has experienced an infection before, if negative he/she hasn't.
3- Only pregnant mothers with an active primary infection can result in congenital toxoplasmosis; mothers with previous infections mount an immune response that protects the fetus. Pregnant mothers, especially those without previous exposure, are encouraged to avoid cats to prevent congenital toxoplasmosis.
4-With adequate immune response, tachyzoites(rapidly dividing) will be transformed into bradyzoites(slowly dividing form), but if the host becomes immunocompromised, reactivation will occur and bradyzoites will transform to tachyzoites

1- Toxoplasmosis cont.

Keywords:
- Cat/undercooked meat
- Chorioretinitis
- IgG avidity

- **Clinical presentation:**
  - **Mostly (70-90%) are asymptomatic** at birth, but are still at high risk of developing abnormalities, especially eye (chorioretinitis)/neurologic disease(MR) later.

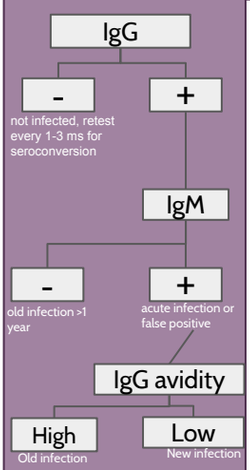
- **Classic triad of symptoms:**

Chorioretinitis	Hydrocephalus	Intracranial calcifications
		

- **Other symptoms include:**
  - Fever, rash, HSM, **microcephaly**,seizures, jaundice, thrombocytopenia, lymphadenopathy.
  - Abortion & Intrauterine death.

Diagnosis & Treatment

Diagnosis



Pregnant mother

- **Serology:**
  -IgM[1]
  -IgG[2]
  -IgG avidity[3]
  -IgG seroconversion[4] compared to booking blood.

Infant

Prenatal

- **Serial ultrasound.** To detect sign of congenital infection
- **PCR.**It is the definitive dx
- Culture.

Postnatal/Newborn

1- Serology:
- IgM
Note: -ve result does not exclude infection
- **High IgG or persistently +ve > 12 months.**

2- PCR

3- Culture

4- Evaluation of infant e.g. neuroimaging

Treatment

- **Spiramycin** macrolide used to treat pregnant women and to **prevent** the transmission of toxoplasma to the fetus but it does **not** treat the fetus if the infection has already occurred
- Pyrimethamine and sulfadiazine use if fetal infection is **confirmed** or maternal infection occurred in **3rd trimester** .Treatment should be shifted to this combination and continued until delivery.After delivery neonate should receive this combination for 1 year.

Prevention

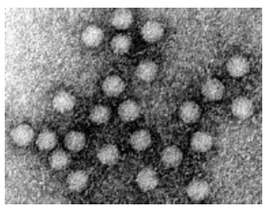
1- Avoid: Exposure to cat feces.
2- Wash: - Hands with soap and water. - Fruits/vegetables - Surfaces that touched fruits/vegetables/raw meat.
3- Cook: all meats thoroughly.

1- **IgM-specific antibodies(Marker of acute infection) can be detected 2 weeks after infection (IgG-specific antibodies usually are negative during this period)**, achieve peak concentrations in 1 month, decrease thereafter, and usually become undetectable within 6 to 9 months.
2- IgG-specific antibodies(Marker of chronic infection/immunity) achieve a peak concentration 3 to 5 months after infection and remain positive indefinitely. The vast majority of patients will have low-positive IgG antibody titers 6 months after the acute infection.
3- **Used to differentiate between old (recurrent) and new (Primary) infections**: IgG produced **early** in infection is **less avid** and binds to T gondii antigens more weakly than do antibodies produced later in the course of infection. **High antibody avidity** indicates an **older** infection
4-seroconversion is the time period during which a specific antibody develops and becomes detectable in the blood. After seroconversion has occurred, the disease can be detected in blood tests.

2- Parvovirus B_{19}

Keywords:
- Hydrops fetalis
- Anemia, rash
- slapped cheek

General info:



- **Family:** Parvoviridae
- Non-enveloped, Icosahedral capsid and SS DNA genome
- Causative agent of Fifth disease[1] (erythema infectiosum)

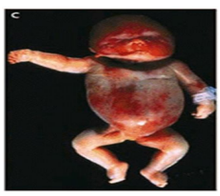
Epidemiology:

- Worldwide distribution
- Humans are known hosts evidence of teratogenicity

Transmission: (Human to Human transmission)

- **Respiratory route.**(Mainly)
- **Blood transfusion.**
- **Transplacental route.**

erythema infectiosum



Hydrops fetalis

Clinical presentation

Acquired infection		Congenital infection
Immunocompetent host	immunocompromised host	Risk of congenital infection is greatest when infection occur in 1st 20 weeks (1st and 2nd trimesters): 1. **Infection in the 1st trimester** → IUD (Intrauterine death) 2. **Infection in the 2nd trimester** → **HF (Hydrops fetalis)**[2] 3. **Infection in the 3rd trimester** → Lowest risk Causes fetal loss through hydrops fetalis, CHF, generalized edema and fetal death.
• Erythema infectiosum (Rash) • Usually self-limiting	-	

Diagnosis & Treatment

	Pregnant mother	Prenatal
Diagnosis	1. Specific IgM. 2. IgG seroconversion.	1. Ultrasound (hydrops) 2. Not grow in cell culture 3. PCR may be used on amniotic fluid.
Treatment	• Intrauterine transfusions	
Prevention	• Hygiene practice • No vaccine (TRIAL)	

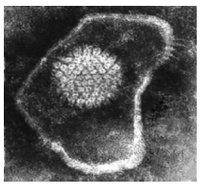
1- AKA Slapped cheek disease. Erythema infectiosum is called "fifth disease" because it is one of the five most common pediatric diseases with rash.
2- Edema due to congestive heart failure caused by severe anemia which is the result of RBC destruction.

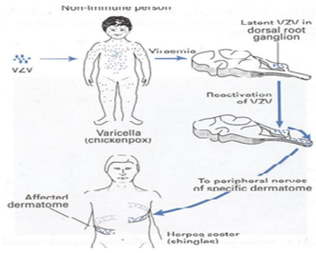
Keywords:
- Vesicular rash, VZIG
- Chickenpox,Shingles

3- Varicella Zoster Virus

General info:

- **Family:** Herpesviridae
- dsDNA , Enveloped, Icosahedral Virus
- 90% of pregnant women already immune





Transmission:

- **Respiratory route**
- **Transplacental route**
- **Direct contact with ruptured varicella vesicles**

Clinical presentation

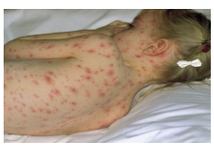
Acquired infection

1- Varicella (Chickenpox) :

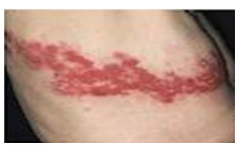
- **Primary** illness
- **Generalized** vesicular rash(itchy)
- Common in children.

2- Zoster (Shingles):

- **Recurrent** infection
- **Localized** painful unilateral vesicular rash
- Common in old people



Chickenpox



Shingles

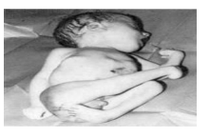
Congenital infection

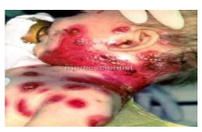
Primary infection carries a greater risk of severe disease, in particular pneumonia.

Intrauterine infections:

1- Congenital varicella syndrome(CVS):

- **1st 20 weeks of Pregnancy**
- The incidence of CVS is ~ 2%
- **Symptoms:**
  - **Scarring of skin**
  - **Hypoplasia of limbs**
  - CNS & Eye defects





2- Neonatal varicella:

- Less than 5 days before delivery → severe disease [1]
- More than 5 days before delivery → mild disease[1]
- Can be prevented by Cesarean delivery

Diagnosis & Treatment

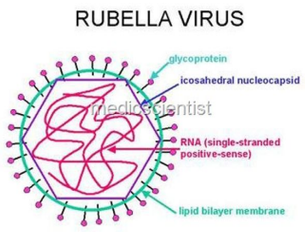
Diagnosis	**Pregnant mother**	**Infant**	
	-Direct from the vesicles: 1- Vesicular fluid for virus isolation. 2- Cells scraping from the base of vesicles → ImmunoFluorescent(Ag) 3- DNA-VZV by PCR **-Serological:** 1- IgM AB	**Prenatal**	**Postnatal**
		1- Ultrasound. 2- VZV DNA in fetal blood or amniotic fluid or placenta villi (usually the sample is amniotic fluid)	1- VZV IgM 2- Virus isolation 3- VZV DNA in VF or CSF (CSF infection)
Treatment	**Acyclovir**		
Prevention	**Pre-exposure**	Varicella live-attenuated vaccines. Contraindicated to use in immunocompromised patients and pregnancy.	
	Post-exposure	**VZIG (Varicella zoster immunoglobulin):** • **Susceptible pregnant women have been exposed to VZV.** • **infants whose mothers develop Varicella < 5 to 2 days after delivery.**	

1- If the maternal rash begins 6 days or more before delivery, her antibody response will have developed and been transferred across the placenta so that the baby does not develop disease. However, the infant is at serious risk if maternal varicella occurs 5 days or less before delivery this allows viraemic spread across the placenta, before antibody is made and transferred to the baby.

4- Rubella Virus

Keywords:
- Routine antenatal screening
- Deafness, PDA.
- Maculopapular rash

General info:



- Family: Togaviridae
- vSS RNA genome, Icosahedral capsid, Enveloped Virus
- Rubella = German measles

Epidemiology:

- Vaccine-preventable disease in human → No longer considered endemic.

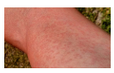
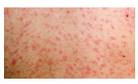
Transmission:

- **Respiratory route. (Mainly)**
- **Transplacental route.**

Clinical presentation

Acquired infection

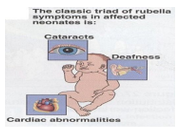
- Ex. Maculopapular rash[1]

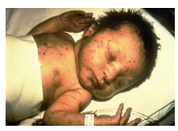



Congenital infection

- Normal → Congenital rubella syndrome (CRS) → IUD (Intrauterine Death)
- Risk of acquiring congenital rubella infection varies and depends on gestational age of the fetus at the time of maternal infection:
  - 0-12 weeks → 70%
  - 13-16 weeks → 20%
  - >16 weeks → infrequent

Congenital rubella syndrome:





- **Triad of abnormalities affect → Ears, Eyes and Heart:**
  - **Ears: Sensorineural hearing loss.(Most common)**
  - **Eyes: Cataracts and glaucoma**
  - **Heart: Cardiac malformations e.g. Patent ductus arteriosus(PDA)**
- Neurologic defects (Less common)
- Others: Growth retardation, **Bone disease**, HSM, Thrombocytopenia, "**blueberry muffin**" lesions

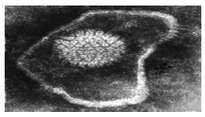
Diagnosis & Prevention

	Pregnant mother	Infant	
		Prenatal	Postnatal
Diagnosis	Serological diagnosis: 1- Rubella specific IgM 2- IgG seroconversion	1- Ultrasound 2- Culture 3- PCR	1- Serology: - **IgM** - Persistence of IgG >9-12 months 2- Culture: 3- PCR
Prevention	• Rubella vaccine (Live attenuated vaccine) • **Routine Antenatal screening: Rubella Specific IgG[2]** ○ Non-immune women → vaccination (avoid pregnancy for 3 months)		

1- A type of rash characterized by a flat, red area on the skin that is covered with small confluent bumps.
2-If pregnant woman is +ve for rubella specific IgG → Means she is immune against rubella infection and there is no risk of congenital rubella syndrome.If she is -ve for rubella specific IgG → Means she is suspscebtlie (non-immune) and is at risk.

5- Cytomegalovirus (CMV)

Keywords:
- Owl's eye, intranuclear inclusion bodies
- Urine



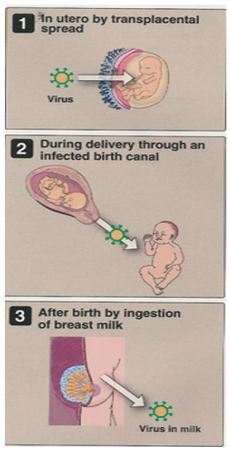
General info:

- **Family:** Herpesviridae
- dsDNA , Enveloped ,Icosahedral Virus.
- Establishes in latent form → reactivation → Recurrent infection.

Epidemiology:

- Human ,worldwide .

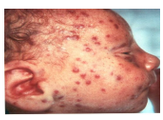
Transmission:



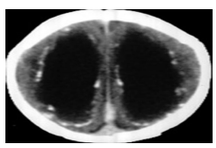
- **Horizontal transmission:**
  - **Young children:** saliva
  - **Later in life:** sexual contact
  - **Blood transfusion & organ transplant**
- **Vertical transmission[2]:**
  - **Primary CMV infection (40%)**
  - **Recurrent CMV infection (~1%)**

Clinical presentation:[1] "Congenital infection"

- **Clinically normal (80%)**
- **Hearing defect and mental retardation (15%)**
- **Death (1%)**
- **Cytomegalic inclusion disease (4%)[3]:**
  - **Symptoms:**



Blueberry muffin" spots



Ventriculomegaly & **calcifications** of congenital CMV

CNS	Eye	Ear	Liver	Lung	Heart	other
microcephaly, periventricular calcification.	chorioretinitis	sensorineural deafness	HSM and jaundice.	pneumonitis	myocarditis	Thrombocytopenic purpura

Diagnosis & Treatment

	Pregnant mother	Infant	
Diagnosis	Serological diagnosis: 1- CMV IgM 2- CMV IgG 3- CMV IgG avidity	Prenatal	Postnatal
		1- Ultrasound 2- Culture 3- PCR	**1- By isolating CMV or detection of its genome in first 3 weeks of life. Body fluid(Sample) : urine, saliva, blood.** **Using:** - Standard tube culture method - Shell vial assay - PCR **2- Histology; Detection of Cytomegalic intranuclear Inclusion Bodies in affected tissue (Owl's eye)** (sight-o-megaly) **3- Serology; CMV IgM**
Treatment	Symptomatic infants → Ganciclovir		
Prevention	• No vaccine, Education about CMV & how to prevent it through hygiene; hand washing		

1- CMV is a well known cause of Infectious mononucleosis-like syndrome [Heterophile AB –ve].(Acquired infection)
2-The risk of intrauterine transmission is much higher during primary maternal CMV infection than recurrent maternal CMV infection
3-Cytomegalic inclusion disease characterized by small baby,hepatosplenomegaly,hematologic disorder including anemia and thrombocytopenia which result in a rash called blueberry muffin spot .it's common sign is intracranial calcification,microcephaly and thrombocytopenia.

Dr.Khalifa

Summary

Introduction:

- Primary infections are worse than recurrent infections,
- Early pregnancy infections are worse than late pregnancy infections..

1- Toxoplasmosis:

- Source: Cat, undercooked meat.
- Transplacental transmission especially in primary infections.
- Triad of symptoms: Chorioretinitis, hydrocephalus, intracranial calcification.
- Diagnosis:
  - Mother: IgM, IgG, IgG avidity, IgG seroconversion.
  - Prenatal: Ultrasound to see transplacentally for any suggestive findings of intrauterine infection e.g. Intrauterine growth retardation, microcephaly.
  - Postnatal: Serology and molecular testing if applicable.

2- Parvovirus:

- Mainly associated with hydrops fetalis especially if it occured in 2nd trimester.
- It's also associated with respiratory infections and erythema infectiosum (Slapped cheek appearance).

3- Varicella - zoster:

- Vaccine preventable disease.
- If patient is previously exposed to chickenpox he will be protected as well, unlike in primary infections in which the mother hasn't been exposed to varicella before, she will transmit it to fetus → Congenital Varicella Syndrome.
- If reactivation((Shingles) occurred during delivery → Neonatal varicella
- Non-immune pregnant women exposed to VZV → Give VZIG

4- Rubella:

- Vaccine preventable disease
- **Routinely** tested antenatal infection.(Rubella Specific IgG only)
- Affects Eye, Ear, Heart.
- Prevention: Rubella vaccine (Live attenuated vaccine)

5- CMV:

- Affects many things e.g. Eye(Chorioretinitis) , potentially hearing loss, heart(Myocarditis) , intracranial calcification.

Diagnosis: almost all have the same diagnosis

- Serological testing for mother and neonate
- **Extra: To sum up for pregnant mother diagnosis:**
  1) - IgG & - IgM → No serological evidence of infection.
  2) - IgG & + IgM → possible acute infection or false-positive IgM result.
  3) + IgG & - IgM → Infection for more than 1 year.
  4) + IgG & + IgM → Possible recent infection within the last 12 months..
- Prenatal: ultrasound

Cases by Dr:

1- A newborn with evidence of chorioretinitis and intracranial calcification. The mother was exposed to cat feces. What's the most likely cause? Toxoplasma gondii

2- A newborn with evidence of hydrops fetalis. The mother had contact with a child who has rash on his face and body. What's the most likely cause? Parvovirus B19

Lecture Quiz

MCQ:

Answers: Q1:C | Q2:A | Q3:C | Q4:C | Q5:B

Q1: This virus causes a mononucleosis-like syndrome caused by a latent herpesvirus; it is often a congenital infection. Large amounts of the virus are excreted in the urine; thus, urine becomes the fluid of choice for diagnosis of this disease which is caused by:
A- Toxoplasma gondii
B- Rubella virus
C- CMV
D- VZV

Q2: A 2-week-old premature male infant is examined in the neonatal intensive care unit, and shows a wide pulse pressure and a holosystolic and holodiastolic murmur. On echocardiography he has blood flow between the left pulmonary artery and the aorta. Which of the following symptoms would the mother have experienced during pregnancy to increase the risk of having a child with this disorder?
A- Maculopapular rash spreading from face to body
B- Mild fever, sore throat, body aches, malaise, and swollen glands
C- Prolonged, persistent paroxysmal cough
D- Vaginal itching and mucopurulent discharge

Q3: There is considerable overlap of signs and symptoms seen in congenital and perinatal infections. In a neonate with "classic" symptoms of congenital cytomegalovirus (CMV) infection, which one of the following tests would be most useful in establishing a diagnosis?
A- CMV IgG titer on neonate's serum at birth
B- CMV IgG titer on mother's serum at birth of infant
C- CMV IgM titer on neonate's serum at birth and at 1 month of age
D- Culture of mother's urine

Q4: Chicken pox is a common disease of childhood. It is caused by which of the following viruses?
A- Cytomegalovirus
B- Rotavirus
C- Varicella-zoster virus
D- Papillomavirus

Q5: Which of the following pathogens require routine antenatal screening test?
A- Toxoplasma gondii
B- Rubella virus
C- CMV
D- VZV

SAQ:

CASE: At birth, a newborn is noted to be unresponsive to verbal stimulation from the doctors, nurses, and his parents. A routine physical examination of the child reveals a split S2 heart sound with an accentuated P2 component (PDA). The newborn has bounding pulses with a wide pulse pressure. After a week the newborn's parents notice that he has developed shortness of breath and respiratory distress. What pathogen did the mother contract during her pregnancy that could explain the newborn's current condition?

Q1: What is the most likely diagnosis?
A: Congenital rubella syndrome

Q2: What pathogen did the mother contract during her pregnancy that could explain the newborn's current condition?
A: Rubella virus

Q4: How is it transmitted?
A: Respiratory, transplacental routes

Q5: How to prevent it?
A: 1- Rubella vaccine (Live attenuated vaccine) 2- Routine Antenatal screening: Rubella Specific IgG

Members Board

- **Team Leaders:**

 **Abdulaziz Alshomar**

 **Ghada Alsadhan**

- **Team sub-leader:**

 **Mohammed Alhumud** (coolest sub leader ever)

- **This lecture was done by:**

 **Mashal Abaalkhail**

 **Note takers:**

- Mashal Abaalkhail
- Rema Alkahtani